Supreme Court, U.S.
FILED
95 28 JUL 3 1995
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No. 95-

IN THE
Supreme Court of the United States
OCTOBER TERM, 1995

SCHERING CORPORATION,
Petitioner,

v.

FOOD AND DRUG ADMINISTRATION,
Respondent.

Petition for Writ of Certiorari to the United States Court of Appeals for the Third Circuit

PETITION FOR WRIT OF CERTIORARI

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QUESTIONS PRESENTED

"Bioequivalence" is the statutory standard of comparable safety and efficacy between a generic drug and the pioneer drug it copies that must be met before the Food and Drug Administration ("FDA") may approve any generic drug for sale in the United States. The bioequivalence requirement was added by, and defined in, the 1984 "Hatch-Waxman Amendments" to the Federal Food, Drug, and Cosmetic Act.

1. Did the court of appeals err in concluding that FDA, by regulation, could attempt to promote generic drug approvals by promulgating a more lenient definition of bioequivalance than that contained in the Hatch-Waxman Amendments?

2. Did the court of appeals wrongly defer to FDA's redefinition of the bioequivalence requirement pursuant to *Chevron U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984), where the redefinition was a significant and unacknowledged departure from the definition codified by Congress, and where the court had already rejected FDA's understanding of the purposes of the bioequivalence requirement as inconsistent with the Hatch-Waxman Amendments?

RULE 29.1 STATEMENT

Petitioner Schering Corporation is a wholly-owned subsidiary of Schering-Plough Corporation. Petitioner has the following non-wholly owned subsidiaries: P.T. Schering-Plough Indonesia; Schering-Plough (Proprietary) Limited (South Africa); Essex Pharmor S.A. (Greece); Fulford (India) Limited; Schering-Plough Korea Corporation; Essex Farmaceutica, S.A. (Colombia); Industria Quimica e Farmaceutica Schering-Plough Ltda. (Brazil); Shanghai Schering Plough Pharmaceutical Company, Ltd. (China).

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OPINIONS BELOW

The opinion of the United States Court of Appeals for the Third Circuit is reported at 51 F.3d 390 (1995), and is reprinted at pages 1a-21a of the Appendix to this Petition ("App."). The opinion of the United States District Court for the District of New Jersey is reported at 866 F. Supp. 821 (1994), and is reprinted at App. 22a-32a.

JURISDICTION

The opinion and judgment of the court of appeals were entered on April 3, 1995. App. 1a. This Court has jurisdiction pursuant to 28 U.S.C. § 1254(1).

STATUTES AND REGULATIONS INVOLVED

The relevant portions of the Federal Food, Drug, and Cosmetic Act, as amended by the Drug Price Competition and Patent Term Restoration Act of 1984, 21 U.S.C. §§ 355(j)(7)(A) and (B), and 355 (*l*), are reprinted at App. 50a. The relevant portions of the regulations of the Food and Drug Administration at issue in this case, 21 C.F.R. § 320.1(a) and (e) (1992), and their predecessor regulations, 21 C.F.R. § 320.1(a) and (e) (1977), are reprinted at App. 52a-53a.

STATEMENT OF THE CASE

This case involves the statutory framework pursuant to which all generic drugs are approved for sale in the United States. Specifically, it involves the statutory requirement that a generic drug be "bioequivalent" to the approved pioneer product which it copies before the generic may be introduced into commerce. The mandatory bioequivalence requirement was first added to the generic drug approval process by the 1984 "Hatch-Waxman Amendments" to the Federal Food, Drug, and Cosmetic Act, which revolutionized the generic drug approval process by expanding dramatically the universe of drugs for which generic copies might be approved. Generic drugs are not subject to full clinical testing for safety and effectiveness. The bioequivalence requirement, which the Hatch-Waxman Amendments not only added but also defined, ensured in the new era that all generic products, despite their limited testing, would be comparable to their pioneer drug products in all material respects.

FDA, which is charged by statute with approving generic drugs pursuant to the standards established by Congress, does not consider the Hatch-Waxman Amendments to establish a definition of bioequivalence which the agency must honor. Rather, believing that approval of generic copies of every pioneer drug is the paramount

objective of the new law, FDA has taken the position that it has discretion to approve generic drugs pursuant to whatever definition of bioequivalence it believes to be appropriate, whether or not that definition is as stringent as the one set out by Congress. This position was reflected in final regulations promulgated in 1992 which changed FDA's long-standing regulatory definition of bioequivalence and which departed from the one definition of bioequivalence set out in the statute.

The regime of administrative discretion to determine the criteria for generic drug approvals that the court of appeals has let FDA create is precisely what existed prior to the Hatch-Waxman Amendments. Imposition of a mandatory, defined bioequivalence requirement changed all that, however, and reflected Congress' assumption of a policymaking role in connection with its comprehensive overhaul of the generic drug approval process. Through the regulation at issue in this case, FDA has sought to recapture the discretion that Congress took from it eleven years ago. Moreover, in the exercise of that purported discretion, FDA has redefined bioequivalence in a manner that is less stringent than what Congress required.

A. The Statutory Scheme Authorizing Approval of Generic Drugs

1. *The ANDA Process*

Prior to 1984, manufacturers desiring to sell a generic copy of a drug approved after 1962 were required to submit a new drug application ("NDA")—the result of a rigorous, time consuming, and expensive process that requires among other things the submission of comprehensive animal and human clinical testing that shows that the drug is "safe" and "effective." *United States v. Generix Drug Corp.*, 460 U.S. 453 (1983); *see* 21 U.S.C. § 355(b)(1)(A); 21 C.F.R. Part 314. The Hatch-Waxman Amendments, Title I of the Drug Price Competition and Patent Term Restoration Act of 1984,

Pub. L. No. 98-417, 98 Stat. 1585, created an *abbreviated* new drug application ("ANDA") process through which FDA could approve generic drug products outside of the full NDA process. Under the 1984 legislation, the manufacturer or distributor of a generic drug product is freed from the clinical trials required of NDA applicants so long as it can demonstrate that the generic is "bioequivalent" to the already-approved "pioneer" drug it copies. *See* 21 U.S.C. § 355(j)(2)(A)(iv), (j)(3)(F). In terms spelled out expressly in the statute, the "bioequivalence" requirement is intended to guarantee that the effectiveness and the safety of the generic drug and the pioneer drug will not differ in any significant way. Bioequivalence is the bridge between the safety and efficacy data provided by the original manufacturer in the full NDA process and the generic copy, which has not been subjected to clinical testing, ensuring that the two products are mutually substitutable. App., *infra*, 11a-12a.

The statutory ANDA process created by the Hatch-Waxman Amendments is different from anything that previously existed. FDA had administratively created a version of the ANDA prior to 1984. Most notably for present purposes, however, under the preexisting regulatory regime no mandatory bioequivalence requirement existed. FDA was free to approve a generic drug based upon whatever showing that it deemed adequate, and the agency had complete discretion to decide on a product-by-product basis if a bioequivalence requirement was appropriate. *See* 21 C.F.R. § 320.50-.52 (1977). Where such a decision was made, however, bioequivalence had the specific, fixed definition set out in FDA's regulations. *See id.* § 320.1(e) (1977). The Hatch-Waxman Amendments completely changed this regulatory structure. That legislation made bioequivalence a mandatory, nonwaivable requirement that had to be satisfied in every case, and as a consequence made bioequivalence of central importance to the statutory scheme. App., *infra*, 15a, 19a, 52a.

2. *The Statutory Bioequivalence Requirement*

Bioequivalence goes beyond a simple static comparison of the chemical compositions of two drug products. Merely assuring an identity between two products' chemical composition does not guarantee that they will be substitutable for one another; differences in manufacture can cause differences in how the product works, and its side effects. *See United States v. Premo Pharmaceutical Lab., Inc.*, 511 F. Supp. 958, 963-65 (D.N.J. 1981) Accordingly, the statutory definition of bioequivalence focuses on the actual absorption of drug products by the body, seeking to ensure that the generic and the pioneer product have comparable safety and efficacy. Bioequivalence is defined in the statute as follows:

> A drug shall be considered to be bioequivalent to a listed drug if—
>
> (i) the *rate and extent of absorption* of the drug do not show a significant difference from the rate and extent of absorption of the listed [pioneer] drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses[.]

21 U.S.C. § 355(j)(7)(B)(i) (emphasis added).[1]

A nearly identical definition in terms of a product's rate and extent of absorption was contained in FDA's own 1977 regulations, *see* 21 C.F.R. § 320.1(e) (1977), which had been in force for fifteen years before being changed by the 1992 regulation challenged in this case. FDA has acknowledged that its former definition of bioequivalence was written in exclusive terms, and agrees that the Hatch-Waxman Amendments codified that defini-

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[1] Section 355(j)(7)(B)(ii), not relevant here, defines bioequivalence for generic controlled release products, whose *rate* of absorption differs intentionally from that of the listed drug. Both subsections are reproduced in the Appendix, infra, at 50a.

tion "in all pertinent respects." J.A. 19, 31.[2] The legislative history of the Hatch-Waxman Amendments is to the same effect, expressly referring to the 1977 regulatory definition as having been codified by the legislation. *See* App. 17a; H.R. Rep. No. 857, 98th Cong., 2d Sess. pt. 1, at 31 (1984) ("1984 House Report"), *reprinted in* 1984 U.S.C.C.A.N. 2647, 2664; 54 Fed. Reg. 28,872, 28,882 (1989). Despite this, FDA contends in this case that the statutory definition of bioequivalence is not an exclusive definition but merely one illustration of how bioequivalence might be established.

Bioequivalence is "essential to the operation of the [Hatch-Waxman Amendments]," and acts "to ensure that generic drugs will be as safe and effective as their pioneer drug counterparts." App., *infra*, 11a, 15a. Its importance as a legislative and a policy matter cannot be denied. From the standpoint of statutory structure, imposition of a mandatory, defined, health and safety standard complements the simultaneous expansion of generic drug approvals.[3] From a medical standpoint, the need for a generic and its pioneer to satisfy the statutory standard of comparability arises whenever one brand of a

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[2] The following references herein to briefs and other filings will be to the record in the court of appeals: "FDA Br." refers to the brief of Food and Drug Administration; "Schering Reply Br." refers to the reply brief of Schering Corp.; and "J.A." refers to the Joint Appendix.

[3] The seriousness with which Congress approached bioequivalence, and required FDA to approach it, is reinforced by the fact that the "faking or doctoring [of] bioequivalence studies required for FDA approval to market generic drugs" is at the core of the recent generic drug scandals. *See Generic Drug Approval Process at the Food and Drug Administration: Hearings Before The Subcomm. on Oversight and Investigations of the House Comm. on Energy and Commerce*, 101st Cong., 2d Sess. 2 (1990) (opening statement of Rep. John D. Dingell). At the same hearing, Rep. Wyden commented: "What citizens want to know is when these drugs are safe and effective and bioequivalence is right at the heart of it." Hearing Tr. 26.

particular prescription medication is substituted for another. This indeed is commonplace, and often results from the practice of "generic substitution" by pharmacies, which can occur without the knowledge of the physician or patient.[4] *See, e.g., Foster v. American Home Prods. Corp.*, 29 F.3d 165, 169 (4th Cir. 1994). The bioequivalence requirement—a showing that the rate and extent of absorption of a pioneer product and its generic copy do not differ significantly—is thus essential to preserve public health and safety in an era of generic substitution. It assures that FDA, in approving an ANDA for an untested generic, a physician, in prescribing a generic, a pharmacist, in substituting a generic for the pioneer drug, and the patient, in using a generic, can be confident that the generic will perform in all material respects like the pioneer. App., *infra*, 11a.

B. FDA's Regulatory Redefinition of Bioequivalence

On July 20, 1989, FDA issued proposed regulations to implement certain provisions of the Hatch-Waxman Amendments, which by then had been in force for almost five years. *See* 54 Fed. Reg. 28,872 (1989). Among the proposals was a regulation purporting to define bioequivalence in terms that departed from both FDA's prior regulation and the text of the Hatch-Waxman Amendments. Although the statute and the then-effective regulations defined bioequivalence in terms of the rate and extent of *absorption* of a product, the new regulation deleted this accepted statutory and regulatory benchmark. Instead of absorption, it focused on the "availability" of a drug at the site of action:

> *Bioequivalence* means the absence of a significant difference in the *rate and extent* to which the active

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[4] "To contain drug costs, virtually every state has adopted laws and/or regulations that encourage the substitution of drug products." FDA, *Approved Drug Products With Therapeutic Equivalence Evaluations* v (13th ed. 1993).

> ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives *becomes available* at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study. . . .

See id. at 28,938 (proposing new 21 C.F.R. § 320.1(e) (1992)) (first emphasis in original). *See* App., *infra*, 53a. Schering filed comments objecting to the proposed regulation, *inter alia*, because of its departure from the statutory definition of bioequivalence. *See* Compl. ¶ 20. FDA finalized its redefinition of bioequivalence without alteration on April 20, 1992. *See* 57 Fed. Reg. 17,950 (1992).

FDA's abandonment of the statutory definition of bioequivalence would profoundly affect the agency's view of its ability to approve ANDAs for generic copies of pioneer drugs, and impact most directly on one class of drug products in which Schering is an active market participant. Schering is a research-based manufacturer of pharmaceutical products which sells, among many others, a variety of products whose effectiveness comes from topical application. These products, including the metered-dose inhaler Proventil®, a medication used in the treatment of asthma, are members of a class referred to as nonsystemically effective drugs, or "NSEDs." For a variety of reasons, establishing the bioequivalence of two NSEDs presents unique problems.[5] Under FDA's proposed regulations, however, these problems no longer exist because absorption—the touchstone of both FDA's

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[5] Absorption is more difficult to measure in the case of NSEDs because of their topical application. Blood concentrations—though necessary to measure in order to evaluate potential, unintended side effects—are smaller than those typically encountered with drugs, like pills, that enter the bloodstream through the digestive process. Proving equivalent topical absorption also presents difficult problems of measurement. The court of appeals stated, however, that there was no information in the record to the effect that proving bioequivalence for NSEDs generally was impossible. App., *infra*, 17a & n.12.

then-current regulations and the statute that codified them —no longer is a factor that must be considered. App., *infra*, 4a.

Schering believed that the decision to deviate from the statutory definition of bioequivalence was in violation of the Hatch-Waxman Amendments, and thus was unlawful. Schering also believed that the statutory bioequivalence standard could not be met for NSEDs given currently-available testing methodologies, and that FDA had relaxed the regulatory requirement in order that generics might nonetheless be approved.[6] The Company accordingly filed a citizen petition with FDA pursuant to 21 C.F.R. § 10.30 seeking, *inter alia*, to have the statutory definition of bioequivalence recognized by the agency and employed in all cases.

After the petition was denied in pertinent part, Schering filed suit in the U.S. District Court for the District of Columbia. The parties filed dispositive cross-motions and, in connection with a subsequently-filed motion for preliminary injunction prompted by an NSED approval, the district court entered judgment in favor of FDA. The court characterized the legal issue presented as "a significant one with legitimate arguments on both sides." App., *infra*, 35a. Applying the analysis of *Chevron U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984), the court concluded that the statute unambiguously required that bioequivalence *not* have an exclusive definition. First, the court observed a difference in wording between the statutory definition of bioequiv-

[6] Earlier in 1989, FDA had issued a "Guidance" to industry that stated the agency's intention to approve ANDAs for certain NSEDs (including Schering's Proventil®) based on a definition of bioequivalence that did not conform to that contained in the Hatch-Waxman Amendments. *See Guidance For In Vivo Bioequivalence Studies of Metaprotaranol Sulfate and Albuterol Inhalation Aerosols (Metered Dose Inhalers)*, Division of Bioequivalence, FDA (February 9, 1989).

alence and the adjacent definition of the related term, bioavailability, which even FDA agreed had an exclusive definition.[7] Bioavailability was defined using the definitional verb "means," which was not employed with respect to bioequivalence. The district court thought this difference was proof that Congress did not also intend that bioequivalence have an exclusive definition. In addition, the district court cited Section 355(j)(6)(A)(i)(III), which requires FDA to publish a list of all approved drugs and state for each whether *in vivo* (in the body) or *in vitro* (laboratory) tests will be adequate to establish bioequivalence. The court believed that the reference to *in vitro* testing "suggests" that bioequivalence did not depend upon evidence of absorption. App., *infra*, 40a-42a.

The district court also reviewed the legislative history. It concluded that Congress intended to "refine and extend" FDA's then-current generic drug approval procedures, and believed these procedures allowed FDA to employ definitions of bioequivalence that were not based upon absorption. The court did not review the FDA regulation, 21 C.F.R. § 320.1(e) (1977), that expressly defined bioequivalence. Rather, it surveyed various regulations regarding acceptable test methodologies that appeared to the court to permit bioequivalence (and bioavailability) to be shown without recourse to absorption. With this understanding, the court concluded in the alternative that FDA's interpretation of the statute was a reasonable one. App., *infra*, 43a-44a.

Schering appealed. Prior to oral argument, FDA's regulation redefining bioequivalence was promulgated in final form. The U.S. Court of Appeals for the District of Columbia Circuit subsequently ruled that this action mooted

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[7] "Bioavailability" refers to the rate and extent of absorption of a *single* drug product. *See* App., *infra*, 50a. Bioequivalence is simply the condition in which the bioavailabilities of *two* products are not materially different. *Id.* Thus, "bioequivalence is universally understood to mean comparable bioavailability." *Id.* at 16a n.10.

the litigation, and it invited Schering to pursue its legal claims in the context of a challenge to the final regulation. *See Schering Corp. v. Shalala,* 995 F.2d 1103 (D.C. Cir. 1993).

C. Proceedings in The District Court

On August 10, 1993, Schering filed suit against FDA in the United States District Court for the District of New Jersey. Schering's suit challenged FDA's regulations purporting to define bioequivalence, contending they were contrary to the plain language of the Hatch-Waxman Amendments, and were arbitrary, capricious, and an abuse of discretion.[8]

The district court issued its opinion on April 26, 1994, without having heard oral argument. The court first rejected FDA's claim (not advanced in the District of Columbia litigation) that Schering lacked standing. FDA argued that Schering's economic interest in seeing that the statutory safety and efficacy requirements were enforced was "antithetical" to the purposes of the Hatch-Waxman Amendments, which the agency saw as reflecting a dominant commitment to ensure that a generic copy of every pioneer drug was immediately approvable. *See* App., *infra*, 28a; FDA Br. 24, 25-27, 39-40, 42. The district court disagreed with FDA's views as to the statute's priorities and upheld Schering's standing to sue, holding that Congress had a "twin desire to insure the safety of the generic drugs approved via the abbreviated procedures." App., *infra*, 29a. On the merits, the district court adopted without elaboration the "reasoning" of the earlier decision of the U.S. District Court for the District of Columbia which had addressed a similar issue of statutory interpretation between the parties but which had subsequently been vacated as moot. *Id.* at 31a.

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[8] Schering sought declaratory and injunctive relief. In addition, it sought a ruling that certain proprietary and trade secret clinical testing data submitted in support of its pioneer NDAs were not yet subject to release pursuant to 21 U.S.C. § 355(*l*).

D. Proceedings in The Court of Appeals

Unlike the district court, which appeared to conclude that the statute is not ambiguous at all, the court of appeals quickly found ambiguity in the statutory language and turned, under the second part of *Chevron*, to a deferential review of the reasonableness of the agency's regulation. The court of appeals began, however, by concurring with the district court that Schering had standing to sue, again rejecting FDA's contention that Schering's economic interest in enforcing the statutory definition of bioequivalence conflicted with the allegedly paramount goal of ensuring that generic copies of every pioneer drug could be approved. The court concluded: "This action to enforce the terms of the Act comports with the congressional purpose that the statutory amendments passed to aid generic drug competition not diminish the safety of commercial drugs." *Id.* at 12a.

As to the merits, the court of appeals also employed the two-part test of *Chevron*. Looking first to the statutory text, the court disagreed that the minor difference in statutory language between the definitions of bioavailability and bioequivalence was significant. Distinguishing *Russello v. United States*, 464 U.S. 16 (1983), the court of appeals focused on the definitional language actually employed with respect to bioequivalence and found it "less precise" but fully consistent with a finding that Congress intended both bioavailability and bioequivalence to be exclusively defined terms. App., *infra*, 13a-15a.

The only other statutory provision cited by the court of appeals was Section 355(j)(6)(A)(i)(III), which requires a listing of whether *in vivo* or *in vitro* laboratory bioequivalence testing methodologies would be required for approval of an ANDA. The court believed that this provision "affirmatively suggests that means other than systemic absorption may be employed to ascertain . . . bioequivalence," and concluded that it "further confounds" the question whether Section 355(j)(7)(B) sets

forth an exclusive definition of bioequivalence. App., *infra*, 16a.

Having concluded that the statute was ambiguous, the court of appeals proceeded to the second part of the *Chevron* test, and asked whether FDA's assertion that Section 355(j)(7)(B) did not limit the agency's discretion to approve generic drugs was a "permissible construction of the Act." In conducting this inquiry, the court noted that the Hatch-Waxman Amendments "generally extend[ed]" the limited administrative procedure for generic drug approvals that existed prior to 1984. The court also cited FDA regulations that addressed potentially permissible "studies and tests," and inferred from these that FDA had previously asserted discretion to accord bioequivalence a flexible definition. For this reason, and because the court believed that the choice of testing methodologies for bioequivalence raised a technical issue, it concluded that it was required to defer to FDA as to whether Congress intended that the statutory bioequivalence requirement be an exclusive definition or merely a "safe harbor" enacted for the benefit of generic drug manufacturers. *Id.* at 5a, 17a-19a.

REASONS FOR GRANTING THE WRIT

Review by this Court is necessary because the court of appeals erred in allowing FDA to deprive the bioequivalence requirement of the one meaning given it by Congress, and because the court's decision is of demonstrable significance to a matter of legitimate national concern—the approval by FDA of safe and effective generic drugs. The decision of the court of appeals affects the entire generic drug approval process, and would allow FDA to free itself from a statutory obligation which Congress deemed, in that court's own words, "essential to the operation" of the statutory scheme. The bioequivalence requirement was added by the Hatch-Waxman Amendments, and defined, in order to be a congressionally-set threshold

of public health and safety that would have to be satisfied in the case of every generic drug approval. FDA, however, has deleted this specific threshold from the equation, substituting for the judicially-enforceable standard of bioequivalence enacted by Congress a grant of virtually unreviewable administrative discretion to employ such less stringent standard as it may deem appropriate. It has claimed the right to pick and choose among statutory commands, accepting a revolutionary increase in its authority to approve generic drugs while rejecting the limitations on that authority that the statute contains.

If the point were only that the decision as to how high the health and safety bar should be set was never for the agency to make in the first place, review by this Court would be warranted; the proper allocation of authority to decide how safe clinically untested generic drugs taken by millions of Americans must be is a matter of patent national concern. But more is at stake, and this Court's intervention is necessary to ensure that the principal change in the generic drug approval process made by Congress in 1984 is not undone by administrative fiat. What FDA has done with its 1992 regulatory redefinition of bioequivalence is take back precisely the discretion that Congress took from it in 1984. While the agency acknowledges its obligation to comply with the statutory "bioequivalence" requirement, it now accepts only the obligation to comply with a statutory requirement whose flexible, indefinite meaning is for it alone to determine. And the acknowledged effect of the new regulation, if not its acknowledged purpose, is to permit FDA to approve generic drugs that could not satisfy the definition of bioequivalence that Congress adopted, or for that matter the definition that even the agency itself had previously employed.

Viewed in terms of the *Chevron* analysis, it is apparent taking into account statutory language, structure, and legislative history, that the bioequivalence requirement of the

Hatch-Waxman Amendments is an exclusive definition, which FDA has no authority to ignore. The court of appeals' contrary interpretation is based upon an analysis that is incomplete and simply fails to construe the statute in the manner which this Court's precedents require. Unlike many statutes, the Hatch-Waxman Amendments dealt forthrightly with the policy decisions inherent in overhauling the generic drug approval process. Congress spoke to the question of how the bioequivalence requirement should be defined, and did not leave "ambiguous" the fundamental issue of whether the statute would or would not give substantive meaning to an essential element of the statutory scheme.

Beyond this, the court of appeals' conclusion that FDA's "safe harbor" theory of bioequivalence is a reasonable one is also wrong, for two reasons. First, as discussed above, it is based almost exclusively on the incorrect belief that the definition of bioequivalence codified by Congress was one which had whatever meaning FDA chose to give it. Second, it gives deference to an interpretation of the statute that focuses too narrowly on promotion of generic competition as the paramount objective and that as a consequence does not give adequate weight to the primacy of the legislation's clear health and safety concerns. The court of appeals indeed reached this very conclusion in rejecting FDA's claim that Schering lacked standing.

This Court's intervention is warranted to bring FDA's authority back within its banks on the important subject of generic drug approvals, and this case presents the appropriate occasion in which to perform the task. NSEDs, like the asthma drug, Proventil®, can be serious medicines used in life-threatening situations. If generic copies of any of them are being approved pursuant to unlawfully lax standards there should be no occasion for delay. Indeed, there is no reason to believe that a preferable vehicle for addressing this important question is

close at hand. Schering is aware of no other court challenge to FDA's regulatory redefinition of bioequivalence. And challenges on an approval-by-approval basis are made less likely because FDA does not typically disclose the definition of bioequivalence that it has applied in approving a generic drug. Schering, by contrast, has been disputing bioequivalence with FDA since 1989 and arrives at this Court with the legal issues cleanly and concretely presented, on appeal from a decision on dispositive cross-motions. If, as Schering believes, FDA is approving generic drugs in violation of its statutory authority, the time to remedy the situation is now.

I. THE THIRD CIRCUIT'S JUDGMENT THAT THE HATCH-WAXMAN AMENDMENTS DO NOT ESTABLISH A JUDICIALLY-ENFORCEABLE STANDARD FOR HEALTH AND SAFETY IN THE APPROVAL OF GENERIC DRUGS BY FDA IS CONTRARY TO THE STATUTE'S PLAIN LANGUAGE, STRUCTURE, AND LEGISLATIVE HISTORY

FDA's regulatory redefinition of bioequivalence is lawful only if consistent with congressional intent. "It is axiomatic that an administrative agency's power to promulgate legislative regulations is limited to the authority delegated by Congress." *Bowen v. Georgetown Univ. Hosp.*, 488 U.S. 204, 208 (1988). Analysis of this question, in turn, is governed by the familiar standards of *Chevron U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984). Where Congress has directly spoken to a question and has expressed its intent clearly, "that is the end of the matter;" the congressional intent must be implemented by agency and court alike. *Id.* at 842-43.

Construction of Section 355(j)(7)(B) begins with the ordinary meaning of the statutory language itself. *Landreth Timber Co. v. Landreth*, 471 U.S. 681 (1985).

Section 355(j)(7) consists in its entirety of the definitions of two interrelated terms, bioavailability and bioequivalence. The statute provides, in pertinent part:

> For purposes of this subsection:
>
> (A) The term "bioavailability" means the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from a drug and becomes available at the site of drug action.
>
> (B) A drug shall be considered to be bioequivalent to a listed drug if—
>
> (i) the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses[.]

The most natural reading of Section 355(j)(7)(B), the bioequivalence provision, is as a definition, and FDA has expressly so characterized it. *See, e.g.*, 54 Fed. Reg. 28,872, 28,882 (1989). No statutory language counsels otherwise. The introductory phrase, "For purposes of this subsection," is of a type commonly used to introduce definitions, and indeed is so used in Chapter II ("Definitions") of the FDC Act itself. *See* 21 U.S.C. § 321 ("For the purposes of this chapter— . . . ."). The statute confers upon FDA no authority to establish alternative, looser definitions of terms so defined nor is there any textual basis, through use of a term such as "including," on which to conclude that the stated conditions of bioequivalence are not exclusive.

Similarly, the operative language with respect to bioequivalence itself—"[a] drug shall be considered to be bioequivalent to a listed drug if . . ."—is broad and mandatory, and is also a formulation used elsewhere in the FDC Act where substantive terms are given an exclusive definition. Indeed, an analogous structure appears in the

principal enforcement sections of the FDC Act—those authorizing FDA action to prevent the sale of adulterated or misbranded drugs or devices. *See* 21 U.S.C. § 351 ("A drug or device shall be deemed to be adulterated . . . [i]f . . . ."); *id.* § 352 ("A drug or device shall be deemed to be misbranded . . . [i]f . . . ."); *see also id.* § 453 (Poultry Products Inspection Act). FDA, without exception of which we are aware, has never obtained relief based on any theory that there are grounds for finding a drug adulterated or misbranded other than those expressly listed in the statute.

The court of appeals did not reject any of this analysis, and indeed reached conclusions that swept away the principal arguments advanced by the district court and FDA. Thus, the court of appeals rejected the district court's conclusion that the minor difference in wording between the statutory definitions of bioavailability and bioequivalence (the former, but not the latter, employs the definitional verb "means") had any significance. It affirmatively found, on the contrary, that the difference did not "preclude[] the conclusion that Congress intended section 355(j)(7)(B) to represent the exclusive standard to determine the bioequivalence of generic drugs to their pioneer drug counterparts." App., *infra*, 15a. The court of appeals can only be faulted on this score for not taking its analysis far enough, and failing to observe that the statutory definition of bioequivalence employs precisely the language and structure used elsewhere in the FDC Act to establish exclusive definitions of key statutory terms.

Similarly, while the court of appeals agreed with the parties that the statutory definition of bioequivalence codified the then-current FDA regulation defining bioequivalence, *id.* at 17a, it never examined that definition, and thus failed to recognize that it was dispositive of the issue at hand. The prior FDA regulation could not more clearly set forth an exclusive definition:

PART 320—BIOAVAILABILITY AND BIOEQUIVALENCE REQUIREMENTS

§ 320.1 Definitions

* * * *

(e) "Bioequivalent drug products" means pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the therapeutic moiety under similar experimental conditions, either single dose or multiple dose. Some pharmaceutical equivalents or pharmaceutical alternatives may be equivalent in the extent of their absorption but not in their rate of absorption and yet may be considered bioequivalent because such differences in the rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body drug concentrations on chronic use, or are considered medically insignificant for the particular drug product studied.

* * * *

21 C.F.R. § 320.1(e) (1977), App., *infra*, 52a. FDA indeed has held this regulation up as an example of how an exclusive definition could be crafted. *See* J.A. 31. Given FDA's agreement that Section 355(j)(7)(B) codifies this regulatory definition "in all pertinent respects," J.A. 19, no claim that the statutory definition was *non*-exclusive can survive.

So, too, the statutory structure also establishes the exclusivity of the definition of bioequivalence. The court of appeals itself recognized that "bioavailability" as set forth in Section 355(j)(7)(A) is a "clearly defined term," and that "bioequivalence is universally understood to mean comparable bioavailability." App., *infra*, 15a-16a & n.10. Schering argued that this linkage between interrelated terms required that bioequivalence also be deemed a

"clearly defined term," with the two adjacent statutory decisions interpreted *in pari materia*. If bioavailability can be understood only in terms of rate and extent of absorption, and bioequivalence *means* comparable bioavailability, in other words, then bioequivalence also can be found only with reference to rate and extent of absorption; if, as all agree, the one is an exclusive statutory definition, then so is the other. But the court of appeals never reached this issue. Rather, after confirming the exclusive definition of bioavailability and its linkage to bioequivalence, the court stumbled, characterizing as "peculiar" the fact that an exclusive definition would be conferred on the term (bioavailability) that was far less important in the statutory scheme. *Id.* at 15a. There is no peculiarity, of course, because Congress intended to confer an exclusive definition on *both* terms. The court of appeals nevertheless terminated its analysis at this point, apparently on the mistaken assumption that the legal question whether Congress intended a statutory definition to be binding on FDA raised a "difficult scientific issue." *Id.* 16a & n.10.

Indeed, the only aspect of statutory language and structure on which the court of appeals relied for its conclusion that the definition of bioequivalence is ambiguous is 21 U.S.C. § 355(j)(6)(A)(i)(III), which the court believed "affirmatively suggests that means other than systemic absorption may be employed to ascertain . . . bioequivalence." App., *infra*, 16a. As a threshold matter, Section 355(j)(6)(A)(i)(III) does not define bioequivalence and is not even a definitional provision. Nor does it govern FDA's decisionmaking in connection with generic drug approvals. Rather, it obligates FDA to publish for every approved drug a statement whether FDA will allow bioequivalence to be shown through *in vivo* (in the body) or *in vitro* (laboratory) tests. The provision provides no guidance as to the meaning of bioequivalence. The court of appeals believed, however, that "[*i*]*n*

vitro tests do not measure absorption," and inferred from the statutory authorization of *in vitro* bioequivalence tests that absorption must not be a necessary part of bioequivalence. *See* App., *infra,* 16a-17a & n.11.

The court's conclusion was wrong because its premise was faulty, as FDA itself has made clear. *In vitro* tests can be "correlated" with *in vivo* data, meaning in such case that an *in vitro* test is probative of everything that could be tested *in vivo.* Indeed, this point was made by FDA itself in responding to a citizen petition filed shortly after passage of the Hatch-Waxman Amendments. As FDA wrote, "[t]he in vitro dissolution studies submitted by the petitioner comparing the petitioner's product to the pioneer product are not correlated to any in vivo bioequivalence studies. They are thus not sufficient to demonstrate the bioequivalence of these products." *See Colmed Laboratories,* FDA Docket No. 85P-0421/CP at 4 (copy appended as addendum to Schering Reply Br.). Because *in vitro* tests may be probative of absorption, their inclusion as a permissible test methodology is not even remotely in conflict with a definition of bioequivalence that all other indicators point to as exclusive.

There is a wealth of textual evidence to the effect that Congress intended to give fixed, substantive content to the definition of bioequivalence. This evidence supports the only conclusion that could be drawn from the record as to Congress' intent. Prior to 1984, FDA was not obligated to require that bioequivalence be shown in connection with any generic drug approval. *See* 21 C.F.R. § 320.50- .52 (1977). Where it was required, bioequivalence had the fixed meaning that FDA regulations gave it. *See* 21 C.F.R. § 320.1(e) (1977). But because requiring bioequivalence was entirely discretionary, FDA as a practical matter possessed, and exercised, authority to approve ANDAs for products that were *not* bioequivalent

to the pioneer products they copied. The Hatch-Waxman Amendments did not codify this practice; they *ended* it.

For certain generic products, including many NSEDs, compliance with the bioequivalence requirement presented a challenge. Prior to the Hatch-Waxman Amendments this was no impediment to approval, since bioequivalence was discretionary.[9] After that legislation imposed a mandatory bioequivalence requirement, however, the question whether FDA would delay generic drug approvals until test methodologies could detect the products' absorption became an issue with which the agency had to deal. FDA's consideration of the issue was based on a view that Congress intended that a generic copy of every pioneer product be immediately approvable, and its decision was to water down the bioequivalence standard so that the impediment no longer existed. This decision still had to be squared with the statutory definition of bioequivalence, and so was born the theory that Section 355(j)(7)(B) established merely a safe harbor from which FDA was free to depart to employ less rigorous standards. The necessary byproduct of this theory was a construction of the Hatch-Waxman Amendments in which bioequivalence lost all substantive content.

The issues raised in this case are, accordingly, no mere debating points, and the importance of the court of appeals' decision extends beyond NSEDs potentially to all pioneer products. The difference between an exclusive definition of bioequivalence and a "definition" of bioequivalence that is merely a safe harbor is all the difference in the world. In the former case, FDA must conform its decisionmaking to a statutory health and safety standard in a manner capable of judicial review: Congress sets the standard and FDA determines whether

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[9] FDA's response to Schering's citizen petition identifies nine NSEDs for which generic drugs were approved prior to 1984 pursuant to criteria that were published in the Federal Register. J.A. 18. *None* required a showing of bioequivalence.

it has been met with respect to a particular generic drug application. In the latter case, the agency determines not only how a standard may be met but what the standard means to begin with: a model of virtually unreviewable discretion. To the extent the court of appeals allows FDA to read out of the Hatch-Waxman Amendments a judicially-enforceable definition of bioequivalence, the agency may again approve generic drugs pursuant to any standard which it deems appropriate. In the process, FDA recaptures the authority Congress took from it: the authority to approve generic drugs that are not *bioequivalent* to their pioneers. Congress could not have changed the law to impose a mandatory, unwaivable bioequivalence requirement, and addressed its meaning, only to intend that the courts allow FDA to determine that the agency is free to do as it wishes after all.

II. FDA'S CONSTRUCTION OF THE HATCH-WAXMAN AMENDMENTS IS NOT A PERMISSIBLE ONE

Having concluded (erroneously, in Schering's view) that the statutory definition of bioequivalence was ambiguous, the court of appeals correctly understood that its job was not over, and that it was required to overrule any construction of the statute that was not "permissible." App., *infra*, 17a (quoting *Chevron*, 467 U.S. at 842-43). Deference to an administrative construction of an ambiguous term is appropriate only where that interpretation "is reasonable in light of the legislature's revealed design." *NationsBank of North Carolina, N.A. v. Variable Annuity Life Ins. Co.*, 115 S. Ct. 810, 813-14 (1995). The court of appeals did not, however, discharge its obligation of judicial review in this case. It made clear errors in reviewing the regulatory history of bioequivalence, and failed to examine or respect the purposes of the bioequivalence requirement.

A. The Court of Appeals Mistakenly Concluded That FDA's Construction Of The Bioequivalence Requirement Was Consistent With Congress' Codification Of FDA's Pre-Hatch-Waxman Authority

The court of appeals considered FDA's construction of the bioequivalence requirement to be reasonable because it believed that construction to be consistent with Congress' intent to extend "generally" the agency's pre-Hatch-Waxman practices. App., *infra*, 18a. In arriving at this conclusion, the court looked to FDA's 1977 regulations (which were in force in 1984) and believed that it found in those regulations evidence that the agency had considered the definition of bioequivalence to be non-exclusive. Assuming for the moment, as did the court of appeals, that Congress intended to codify FDA's prior practices *in toto*, the court's conclusion would be wrong for the reasons stated in the previous section: FDA historically had not viewed bioequivalence as it now claims, but instead when it chose to require bioequivalence gave that term a fixed, definite meaning, as its own 1977 regulatory definition of the term makes plain. *See* App., *infra*, 52a.

Oddly, in searching for FDA's understanding of the bioequivalence requirement in 1984, the court of appeals did not review the best available evidence: the regulatory definition itself. Rather, the court focused on the fact that in certain *non-definitional* sections of the same regulation FDA listed "several studies and tests required for approval" which, presumably, the court believed reflected an ability to employ different definitions of bioequivalence. *Id.* at 19a. But surely this is irrelevant. Schering does not dispute that, once FDA had decided to require a showing of bioequivalence with respect to a particular ANDA, it had discretion to determine the technical question of what "studies and tests" it wanted applicants to conduct. What Schering does dispute is that, having given bioequivalence an exclusive definition in an adjoining

regulation, FDA was free to make applicants satisfy a different one.

B. The Court of Appeals Was Wrong To Defer To A Construction Of The Bioequivalence Requirement That Conflicted With Congress' Intent

Deference should not be paid to FDA's construction of the bioequivalence requirement for the additional reason that FDA has fundamentally misunderstood Congress' purpose in imposing the requirement in the first place, overemphasizing pro-generic commercial interests and underemphasizing the paramount health and safety goals of the statute. FDA advised the court of appeals that, in its view, "[t]he bioequivalence provisions of the Hatch-Waxman Amendments were intended to ease the entry of generic drugs into the market, not constrain competition." FDA Br. at 42. This conception of the bioequivalence requirement was consistent with FDA's belief that any construction of the statute that interfered with the supposed imperative to approve a generic copy of every pioneer product would have to give way. *See, e.g., id.* at 26 (rejecting any construction of bioequivalence that was not capable of being satisfied for every pioneer drug in 1984).

The court of appeals, however, would have none of it. The court rejected FDA's belief that the bioequivalence requirement existed to "ease" generic drug approvals and recognized, to the contrary, that maintenance of the statutory health and safety standard took precedence over the commercial goals of the statute.[10] FDA indeed held a skewed view of the purpose of the bioequivalence requirement. The question presented under the second part of the *Chevron* test, accordingly, is whether it is appropriate for a court to defer to an agency that has such

[10] As the court of appeals stated, "the fact that actions by [pioneer drug manufacturers] may thwart the competing congressional purpose of easing the entry of generic drugs into the market is subsumed by the overriding necessity of ensuring public access to safe commercial drugs." App., *infra*, 12a-13a.

a demonstrably incorrect view of the law. Clearly the answer to that question is no.

It is long-settled that courts are obligated to review regulations to ensure that the agency has considered the right factors in reaching its decision, and to vacate regulations as arbitrary and capricious where "the agency has relied on factors which Congress has not intended it to consider, entirely failed to consider an important aspect of the problem, . . . or is so implausible that it could not be ascribed to a difference in view or the product of agency expertise." *Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto Ins. Co.*, 463 U.S. 29, 43 (1983); *cf. Citizens to Preserve Overton Park, Inc. v. Volpe*, 401 U.S. 402, 416 (1971). The principal source of guidance to the agency must, of course, be its enabling statute. *Pension Benefit Guaranty Corp. v. LTV Corp.*, 496 U.S. 633, 645-47 (1990); *Brewer v. Madigan*, 945 F.2d 449, 457 (1st Cir. 1991). Regulations that would alter the policy choices made by Congress must be struck down. *American Textile Mfrs. Inst. v. Donovan*, 452 U.S. 490, 509 (1981) ("Any [regulatory] standard based on a balancing of costs and benefits by the Secretary that strikes a different balance than that struck by Congress would be inconsistent with the [statutory] command . . . ."); *see* Laurence H. Silberman, *Chevron-The Intersection Of Law And Policy*, 58 Geo. Wash. L. Rev. 821, 827-28 (1990) ("In either the second step of *Chevron* or in arbitrary and capricious review, the court often asks itself whether the agency considered and weighed the factors Congress wished the agency to bring to bear on its decision.").

It is indeed for agencies and not for courts to balance competing statutory interests so as best to serve congressional intent. But the judicial role exists to ensure that agencies take the correct factors into account, and do not weigh them in a manner demonstrably contrary to Congress' aims. "If the [agency's] choice represents a reasonable accommodation of conflicting policies that

were committed to the agency's care by the statute, we should not disturb it unless it appears from the statute or its legislative history that the accommodation is not one that Congress would have sanctioned." *Chevron*, 467 U.S. at 845 (quoting *United States v. Shimer*, 367 U.S. 374, 383 (1961)). Here, FDA's construction is based upon a lopsided view of the bioequivalence requirement that the court of appeals itself concluded Congress had not intended. *Chevron* cannot mean that a court faced with so demonstrably an incorrect vision of Congress' intent is powerless to intervene.

CONCLUSION

For the foregoing reasons, the Petition For Certiorari should be granted.

Respectfully submitted,

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APPENDIX A

Filed April 3, 1995

UNITED STATES COURT OF APPEALS
FOR THE THIRD CIRCUIT

No. 94-5366

SCHERING CORPORATION,
Appellant

v.

FOOD AND DRUG ADMINISTRATION

Appeal from the United States District Court
for the District of New Jersey
(D.C. Civ. No. 93-cv-03493)

Argued
January 24, 1995

Before: MANSMANN, HUTCHINSON and MCKEE.
Circuit Judges.

(Filed April 3, 1995)

OPINION OF THE COURT

MANSMANN, *Circuit Judge*.

The issue before us, brought in the context of a pioneer drug [1] manufacturer's challenge to the propriety of FDA approval of non-systemically effective generic drugs pursuant to an abbreviated approval process, is one of first impression in the courts of appeals. We must determine whether the bioequivalence requirements, set forth in section 355(j)(7)(B) of Title I of the Drug Price Competition and Patent Term Restoration Act of 1984 (the "Act"), Pub. L. No. 98-417, 98 Stat. 1585 (1984), otherwise known as the "Hatch-Waxman Amendments" to the Food, Drug and Cosmetic Act (the "FDCA"), are the exclusive means for determining the bioequivalence of generic drugs approved pursuant to the abbreviated new drug application procedure ("abbreviated application" or "ANDA") embodied in that Act. 21 U.S.C.A. § 355(j) (West Supp. 1994). A bioequivalent generic drug is one that the FDA has determined to be as safe as the pioneer drug it copies.

We decide this issue in the context of a challenge by Schering Corporation, a research-based manufacturer and distributor of pharmaceutical products, to the Food and Drug Administration's final regulation implementing the ANDA provisions of the Act. The FDA regulation at issue, codified at 21 C.F.R. § 320.1(e) (1994), was promulgated in 1992 to implement the bioequivalence requirements for generic drugs approved under the abbreviated application procedure. Schering charges that the FDA impermissibly broadened the exclusive statutory definition of bioequivalent by substituting the statutorily prescribed measurement of drug "absorption" with a measurement which calculates when the drug becomes

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[1] A pioneer drug is the first drug product containing a particular active ingredient to obtain FDA approval for a specified use. *See* 21 U.S.C.A. § 355(b) (West Supp. 1994).

"available at the site of drug action." *See* 21 U.S.C.A. § 355(j)(7)(B) (West Supp. 1994) ; 21 C.F.R. § 320.1(e) (1994).

The district court entered summary judgment in favor of the FDA, holding that section 355(j)(7)(B) is not the exclusive means for determining the bioequivalence of a generic drug to its pioneer drug counterpart. On Schering's appeal, we find the language of 21 U.S.C.A. § 355(j)(7)(B) (West Supp. 1994) ambiguous and consistent with *Chevron U.S.A. Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984), we hold that the FDA regulation at 21 C.F.R. § 320.1(e) (1994) is a permissible construction of that statute. Accordingly, we will affirm the judgment of the District court.

I.

To receive approval under an abbreviated new drug application, a generic drug manufacturer must establish that its drug is the bioequivalent of a pioneer drug. 21 U.S.C.A. § 355(j)(2)(A)(iv) (West Supp. 1994). The Act provides:

> A drug shall be considered to be bioequivalent to a listed drug [2] if—
>
> (i) the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same . . . dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses;
>
> or

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[2] A listed drug is a drug that has been approved for safety and effectiveness under 21 U.S.C. § 355(c) prior to September 24, 1984, which was included on a published list of drugs approved by the FDA. *See* 21 U.S.C.A. §§ 355(j)(2)(A)(i) and (j)(6)(A)(i)(I) (West Supp. 1994).

> (ii) the extent of absorption of the drug does not show a significant difference from the extent of absorption of the listed drug when administered at the same . . . dose of the therapeutic ingredi ent under similar experimental conditions . . . and the difference from the listed drug in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use and is considered medically insignificant for the drug.

21 U.S.C.A. § 355(j)(7)(B) (West Supp. 1994). The FDA regulation at issue implementing subpart (i) of this statutory provision defines bioequivalence in relevant part as "the absence of a significant difference in the rate and extent to which the active ingredient . . . becomes available at the site of drug action when administered at the same . . . dose under similar conditions in an appropriately designed study." 21 C.F.R. § 320.1(e) (1994). Schering does not challenge the regulation implementing subpart (ii) of the above-quoted provision regarding intended differences in the rate of availability from a listed drug.

Schering manufactures and distributes the pioneer drugs Proventil[RM], an aerosol metered-dose asthma inhaler, and Lotrimin[RM], an antifungal cream, both of which are non-systemically effective drugs ("NSEDs"). NSEDs are products that derive their effectiveness from application directly at the site of drug action, such as by application of an ointment to the skin or inhalation of a drug-containing mist into the lungs, rather than through systemic absorption into the bloodstream. Schering challenges the regulatory definition of bioequivalence as impermissibly substituting the statutory reference to the rate and extent of drug absorption with a reference to the rate and extent to which a drug becomes available at the site of drug action. Schering argues that section 355(j)(7)(B) unam-

biguously sets forth the exclusive definition of bioequivalence; therefore, all generic drugs seeking approval pursuant to the ANDA process must meet one of the two criteria set forth in section 355(j)(7)(B) to establish bioequivalence, both of which require absorption [3] data.

The FDA disputes that absorption data is required to establish the bioequivalence of generic NSEDs. Bioequivalence occurs when two drugs possess the same efficacy. The FDA argues that bioequivalence can be measured by using one of several methodologies, including absorption; however, the appropriate method used depends on the type of drug under consideration for approval. The FDA, therefore, views section 355(j)(7)(B) as delineating a "safe harbor" or circumstances when the FDA *must* recognize a generic drug as the bioequivalent of a pioneer drug, but not as a limitation on the criteria the FDA may use to ascertain bioequivalence.

In 1989, Copley Pharmaceutical, Inc., filed an abbreviated application pursuant to section 355(j) to manufacture and market a generic copy of Proventil[RM]. On December 4, 1989, Schering filed a Citizen Petition with the FDA, pursuant to 21 C.F.R. § 10.25 (1990), seeking *inter alia* a declaration that section 355(j)(7)(B) set forth the exclusive means for determining bioequivalence in terms of the rate and extent of drug absorption and

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[3] At oral argument, Schering clarified that it defines "absorption", relying in part on comments of the FDA accompanying the Final Abbreviated New Drug Application Regulations, to mean that "[a]ll drugs must be absorbed through some physical barrier to reach the site of drug action, even if that absorption involves only dispersion into a body fluid pool or entry into surface cells." Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17,950, 17,972 (1992) (codified at 21 C.F.R. §§ 2, 5, 10, 310, 314, 320 and 433). Schering argues that the FDA interprets too narrowly section 355(j)(7)(B) "absorption" as systemic absorption, resulting in the FDA's unwarranted conclusion that Schering seeks to prevent an entire class of drugs, NSEDs, from being approved through the ANDA process.

that absorption data could not as a practical matter be provided for NSEDs such as Proventil[RM] or its generic counterpart because they do not depend on absorption to achieve their desired effect. The FDA responded to Schering's Citizen Petition on June 29, 1990, denying the requested relief. The FDA stated its position that a generic drug may satisfy the statutory bioequivalence requirement even if it does not meet the absorption criteria set forth in section 355(j)(7)(B). This constituted final agency action from which relief could be sought in a United States District Court. *See* 21 C.F.R. § 10.45(d) (1990).

Schering thus sought review of the FDA's response to its Citizen Petition in the United States District Court for the District of Columbia. While cross-motions for summary judgment were pending, the FDA approved Copley's ANDA to manufacture and market a generic version of Proventil[RM]. Schering immediately filed a motion for preliminary injunction to enjoin the FDA's approval of the generic version of Proventil[RM], which the district court denied. The district court granted the FDA's motion for summary judgment, concluding that section 355(j)(7)(B) did not set forth the exclusive means for determining bioequivalence and that the FDA's interpretation of the statute as permitting alternative methodologies to establish bioequivalence was reasonable. *Schering Corp. v. Sullivan*, 782 F. Supp. 645, 650 (D.D.C. 1992), *vacated as moot sub nom. Schering Corp. v. Shalala*, 995 F.2d 1103 (D.C. Cir. 1993).

Schering appealed the district court's judgment to the United States Court of Appeals for the District of Columbia Circuit, challenging the legal conclusion that the FDA is not limited to the absorption criteria set forth in section 355(j)(7)(B) to determine the bioequivalence of a generic drug to its pioneer drug counterpart. During the pendency of the appeal, the FDA issued final regulations regarding the ANDA process, including its definition of the term bioequivalence. 57 Fed. Reg. 17,949-

18,001 (1992). The court of appeals determined that the newly promulgated 1992 regulations rendered moot Schering's appeal based on the FDA's Citizen Petition Response and, therefore, vacated the district court opinion. *Schering Corp. v. Shalala*, 995 F.2d 1103 (D.C. Cir. 1993). The court recognized that Schering's challenge to the FDA's construction of section 355(j)(7)(B) should be brought in the context of the new regulations.

On August 10, 1993, Schering filed this present action in the United States District Court for the District of New Jersey, challenging the FDA's regulation at 21 C.F.R. § 320.1(e) (1994) as impermissibly broadening the statutory definition of bioequivalent.[4] Converting the FDA's motion to dismiss to a motion for summary judg-

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[4] Schering also requested injunctive relief precluding the FDA from releasing Schering's safety and efficacy data pursuant to section 355(l)(5). Section 355(l)(5) provides:

> Safety and effectiveness data and information which has been submitted in an application under subsection (b) of this section for a drug and which has not previously been disclosed to the public shall be made available to the public, upon request, unless extraordinary circumstances are shown—
>
> . . . .
>
> (5) upon the effective date of the approval of the first application under subsection (j) of this section which refers to such drug or upon the date upon which the approval of an application under subsection (j) of this section which refers to such drug could be made effective if such an application had been submitted.

21 U.S.C.A. § 355(l)(5) (West Supp. 1994). Schering's argument in this regard is dependent upon a finding in favor of Schering on the merits of its challenge. Schering argued that since NSEDS cannot be approved pursuant to the ANDA process, trade secret data for pioneer NSEDS cannot be released pursuant to section 355(l)(5) because there is no known testing method that would permit the statutory bioequivalence requirement to be met. In light of its ruling in favor of the FDA on the merits, the district court denied Schering's request for injunctive relief precluding the FDA from releasing Schering's safety and efficacy data.

ment in light of the parties' submissions outside the briefs,[5] the court granted the FDA's motion regarding the merits of Schering's claims and denied Schering's motion for summary judgment. *Schering Corp. v. Food and Drug Admin.*, 866 F. Supp. 821 (D.N.J. 1994).

The district court found that Schering had standing to maintain this action. The district court determined and the FDA did not contest that Schering's loss of monopoly profits sustained the injury-in-fact requirement for Article III standing. As to prudential standing, the district court found that Schering's interests in protecting profits was congruent with one of the two congressional concerns prompting the passage of the Act—ensuring the safety of generic drugs.[6] The district court then adopted the reasoning of Judge Boudin in *Schering Corp. v. Sullivan*, 782 F. Supp. 645 (D.D.C. 1992), *vacated as moot sub*

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[5] The FDA filed a motion for judgment on the pleadings on grounds that Schering lacked standing to challenge the regulation or, alternatively, that Schering failed to state a claim upon which relief could be granted. Schering filed a motion for summary judgment based on its view that the Act unambiguously defines bioequivalent. Schering submitted the FDA's Citizen Petition Response and comments to the FDA final ANDA regulations with its brief in support of its motion for summary judgment. The FDA submitted the relevant provisions of the FDA regulations with its memorandum in support of its motion for judgment on the pleadings and in opposition to Schering's motion for summary judgment. The FDA also submitted the Declaration of Donald B. Hare, the Special Assistant for the Director, Office of Generic Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, in support of its reply to Schering's opposition to the FDA's motion for judgment on the pleadings.

[6] Schering also asserted it had standing pursuant to FDA regulations that provide an "interested person" the right to seek judicial review of final agency action. *See* 21 C.F.R. § 10.45(d). The district court found that an administrative agency by regulation could not circumvent the requirements for Article III or prudential standing for an action brought pursuant to the Federal Administrative Procedures Act, 5 U.S.C. § 702.

dom, Schering Corp. v. Shalala, 995 F.2d 1103 (D.C. Cir. 1993), concluding that section 355(j)(7)(B) did not set forth the exclusive definition of bioequivalent.[7]

Schering appeals the district court's finding that section 355(j)(7)(B) is a non-exclusive provision for determining whether a generic drug is the bioequivalent of the pioneer drug it copies and the denial of its request to enjoin the FDA from disclosing confidential safety and effectiveness data for Schering's pioneer NSEDs. Schering also raises the issue of the propriety of the district court's conversion of the FDA's motion for judgment on the pleadings into a motion for summary judgment without providing Schering a "reasonable opportunity" to respond to the Declaration of Donald Hare filed concurrently with the FDA's final brief in support of its motion.

We turn first to the threshold issue of Schering's standing to challenge the FDA regulation given the FDA's contention that Schering lacks prudential standing.

II.

Article III standing is satisfied when a plaintiff demonstrates that it has suffered an actual or threatened injury as a result of the defendant's conduct which is capable of redress. *Wheeler v. Travelers Ins. Co.,* 22 F.3d 534, 537-38 (3d Cir. 1994). Prudential standing requires that Schering assert legal interests of its own within the "zone of interests" the Act protects, thereby ensuring that the federal courts will not be adjudicating

[7] Judge Boudin had determined that the intent underlying section 355(j)(7)(B) was clear from the language, structure and legislative history of the Hatch-Waxman Amendments to the FDCA; that Congress intended that the FDA retain its historically wide discretion in determining bioequivalence. Even if the statute were ambiguous, Judge Boudin nevertheless would uphold the FDA's interpretation as reasonable in light of the FDA's practice of accepting alternative showings of bioequivalence and the absence of evidence that Congress intended to override that practice.

abstract questions of wide public significance that are nothing more than generalized grievances. *Id.* The "zone of interest" test is a guide to determine whether a particular plaintiff may bring an action pursuant to the Administrative Procedures Act, 5 U.S.C.A. § 702,[8] to complain of a particular agency action. *Clarke v. Securities Industry Ass'n*, 479 U.S. 388, 399 (1987). When, as here, the plaintiff is not itself subject to the challenged agency action, the zone of interests test denies a right of review if the plaintiff's interests are only marginally related to the purpose of the statute. *Id.* The test, however, is not so stringent that it requires the would-be plaintiff to be specifically targeted by Congress as a beneficiary of the statute. *Id.* at 399-400. Our review of the district court's judgment is plenary. *Polychrome International Corp. v. Krigger*, 5 F.3d 1522 (3d Cir. 1993).

The FDA did not contest before the district court and does not contest here that Schering's potential loss of monopoly profits upon FDA approval of a competitive generic substitute is sufficient to meet the Article III injury-in-fact standing requirement. Instead, the FDA challenges the district court's finding that Schering met prudential standing requirements to assert a claim to protect its loss of monopoly profits.

Plaintiffs who suffer economic injury from unlawful competition may fall within the "zone of interests" protected by "entry-restricting" statutes to establish prudential standing. *See, e.g., First Nat'l Bank and Trust Co. v. Nat'l Credit Union Adm.*, 988 F.2d 1272, *cert. denied sub nom, AT&T Family Fed'l Credit Union v. First Nat'l Bank & Trust Co.*, —— U.S. ——, 114 S. Ct. 288 (1993) (investment bankers had standing to chal-

[8] Section 702 provides:

> A person suffering legal wrong because of agency action, or adversely affected or aggrieved by agency action within the meaning of a relevant statute, is entitled to judicial review thereof. . . .

lenge a ruling by the Comptroller of Currency that permitted banks to overcome a statutorily imposed limitation on their securities underwriting and investment activities, which was designed to protect bank depositors from risky bank activities and not to protect investment bankers from competition). In such cases, the plaintiff's interests in protecting its competitive position may coincide with the legislative purpose of imposing an entry restriction. When a plaintiff's protection of its competitive interests, however, fails to coincide with the legislative purpose of the statute it seeks to enforce, prudential standing will not lie. *See, e.g., Calumet Industries, Inc. v. Brock,* 807 F.2d 225 (D.C. Cir. 1986) (chemical manufacturers lacked standing to challenge Occupational Safety and Health Administration ("OSHA") Notice of Interpretation regarding labeling requirements to protect their sales and profits given that interest protected by the Occupational Health and Safety Act is worker safety, not competitive interests); *Hazardous Waste Treatment Council v. Environmental Protection Agency,* 861 F.2d 277 (D.C. Cir. 1988), *cert. denied,* 490 U.S. 1106 (1989) (national trade organization of firms engaged in treatment of hazardous waste lacked prudential standing to challenge EPA regulations as not fully complying with requirements of the Resource Conservation and Recovery Act ("RCRA") given that RCRA evidences congressional intent to foster cleaner environment but does not evidence intent to benefit pecuniary interests of such firms).

The bioequivalence requirement set forth in section 355(j)(7)(B) acts as a market entry restriction imposed to ensure that generic drugs will be as safe and effective as their pioneer drug counterparts. *See* Vol. 130 Part 17 Cong. Rec. 24,425 (1984) (statement of Rep. Skelton: "The approval process . . . assures that, while generic drugs will be made more quickly available, the quality and effectiveness of those drugs will not be reduced."). *See also* H.R. Rep. No. 98-857, 98th Cong., 2nd Sess.

pt. I, *reprinted in* 1984 U.S.S.C.A.N at 2647-68 ("[G]eneric copies of any drugs may be approved if the generic is the same as the original drug or so similar that FDA has determined the differences do not require safety and effectiveness testing"). Schering's interest, as a pioneer drug manufacturer seeking to enforce the entry restrictions imposed upon generic drug manufacturers using the ANDA process, is aligned with one of the interests Congress intended to protect or benefit through the passage of the Act. In *Tri-Bio Laboratories, Inc. v. Food and Drug Admin.*, we recognized the balance of interests struck by Congress in enacting the Drug Price Competition and Patent Term Restoration Act as follows:

> This statute attempts to balance the interests of the generic drug manufacturers, who sought to avoid unnecessary testing, against the research investments of the pioneer manufacturers, at the same time mindful of the public need for safe commercial drugs. The 1984 Amendments, which applied only to human drugs, reflect a statutory compromise of the competing concerns.

836 F.2d 135, 139 (3d Cir. 1987), *cert. denied,* 488 U.S. 818 (1988) (veterinary drugs were not within the purview of the 1984 Amendments to the Food, Drug and Cosmetic Act). This action to enforce the terms of the Act comports with the congressional purpose that the statutory amendments passed to aid generic drug competition not diminish the safety of commercal drugs. Pioneer drug manufacturers are well-positioned to monitor FDA regulations implementing statutorily mandated requirements for the abbreviated approval of generic competitor drugs when it is their pioneer drug the generic manufacturer seeks to copy. They possess the scientific data to recognize when the FDA may stray from the legislatively mandated testing requirements that impact the safety and effectiveness of the generic drug. The fact that actions by such parties may thwart the competing

congressional purpose of easing the entry of generic drugs into the market is subsumed by the overriding necessity of ensuring public access to safe commercial drugs. As such, we find that the district court did not err in holding that Schering was a suitable challenger to the FDA regulations implementing section 355(j)(7)(B).[9]

III.

In *Chevron U.S.A. Inc. v. Natural Resources Defense Council, Inc.*, 567 U.S. 837 (1984), the Supreme Court set forth standards for our review of an agency's interpretations of the statute it is entrusted to administer. We exercise plenary review of the construction of statutes administered by an agency when Congress has unambiguously addressed the question at issue. *Chevron*, 467 U.S. at 842-43; *Passaic Valley Sewerage Commissioners v. United States Department of Labor*, 992 F.2d 474, 478 (3d Cir.), *cert. denied*, —— U.S. ——, 114 S. Ct. 439 (1993). If, however, the statute is ambiguous regarding the issue, our task is to determine whether the agency's interpretation is a permissible construction of the statute. *Chevron*, 467 U.S. at 842-43. Obviously, our first step here is to review the text of section 355(j)(7)(B) to determine whether the intent of the statute is unambiguous; *i.e.*, whether the text clearly reflects Congressional intent to make it the *exclusive* means by which the bioequivalence of a generic drug may be established for purposes of the ANDA procedure.

A.

Section 355(j)(7)(B) provides in relevant part:

> (B) A drug shall be considered to be bioequivalent to a listed drug if—

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[9] We note that Schering raised alternative bases for standing; however, we need not reach those issues given our ruling that Schering's competitor interest provided standing to sustain its challenge to the FDA regulations.

> (i) the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses; or

21 U.S.C.A. § 355(j)(7)(B)(i) (West Supp. 1994). The language on its face, as Judge Boudin observed, is neutral—it neither imposes nor forecloses the interpretation that it is an exclusive definition of bioequivalent. *See* 782 F. Supp. at 645.

Even when reviewed in the context of the entire Act, we find the language of the section to be ambiguous. Congress delineated two terms within section 355(j)(7), "bioavailability" and "bioequivalent." Section 355(j)(7)(A) provides in relevant part:

> (7) For purposes of this subsection:
>
> > (A) The term "bioavailability" means the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from a drug and becomes available at the site of drug action.

21 U.S.C.A. § 355(j)(7)(A) (West Supp. 1994). Judge Boudin relied upon a comparison of the language used to introduce each of these terms to support his conclusion that section 355(j)(7)(B) did not set forth an exclusive definition of bioequivalent. He relied on the rule of statutory construction that when one of two closely related subsections possesses limiting language that the other lacks, we may presume the omission was intentional. *See Russello v. United States*, 464 U.S. 16, 23 (1983) (determining the meaning of "interest" as used in 18 U.S.C. § 1963(a)(1) was the broader ordinary meaning of the word rather than the more restrictive term "interest in enterprise" that was used in 18 U.S.C. § 1963(a)(2)).

See also Pension Benefit Guaranty Corp. v. White Consolidated Industries, Inc., 998 F.2d 1192, 1201 (3d Cir. 1993), *cert. denied*, —— U.S. ——, 114 S. Ct. 687 (1994) (court declined to read a predecessor liability provision into 29 U.S.C. § 1362 when another section of the same statute, section 1369, articulated a rule of predecessor liability).

We find that the disputed language in section 355(j)(7), which is a definitional section, is not as susceptible to clarification through application of this rule of construction as were the specific statutory terms in *Russello* and *White Consolidated Industries*. We recognize that the language of sub-section (j)(7)(A) that " 'bioavailability' *means* the rate and extent" is indicative of an exclusive definition. *See Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 630 (1973). Nonetheless, Congress' use of the less precise phrase *"shall be considered to be"* to introduce "bioequivalent" does not compel the conclusion, as was the case in *Russello*, that Congress intended section 355(j)(7)(B) to be non-exclusive and as merely establishing a "safe harbor" mandating the approval of some generic drugs. It is not apparent to us that the use of a different introductory phrase precludes the conclusion that Congress intended section 355(j)(7)(B) to represent the exclusive standard to determine the bioequivalence of generic drugs to their pioneer drug counterparts. This conclusion is buttressed by a comparison of the impact the terms have on the operation of the Act.

"Bioavailability," though clearly a defined term, is not referenced elsewhere in the Act and has no apparent impact on the operation of the Act. "Bioequivalent," however, is essential to the operation of the Act. All ANDAs submitted to the FDA pursuant to section 355(j) must contain "information to show that the new drug is bioequivalent to the listed drug." 21 U.S.C.A. § 355(j)(2)(A)(iv) (West Supp. 1994). Indeed, it is peculiar

that Congress defined "bioavailability," a term that has no apparent impact on the operation of the Act; the parties' explanations have not clarified this difficult scientific issue.[10]

B.

Section 355(j)(6)(A)(i)(III), which affirmatively suggests that means other than systemic absorption may be employed to ascertain the bioequivalence of a generic drug, further confounds the issue of the exclusivity of section 355(j)(7)(B). 21 U.S.C.A. § 355(j)(6)(A)(i)(III) (West Supp. 1994). That section vests the FDA with discretion to determine whether *in vitro* or *in vivo*[11] bioequivalence studies, or both, will be required for the approval of generic drugs under the abbreviated application process. *Id.* Vesting the FDA with discretion to authorize *in vitro* tests to establish bioequivalence supports the FDA's interpretation that Congress contemplated the approval of generic drugs through the ANDA

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[10] The parties instruct us that bioequivalence is universally understood to mean comparable bioavailability, suggesting that there is some relationship between the terms that is essential to our interpretation of section 355(j)(7)(B). This notion, however, is thwarted by the dependency of the parties' explanations on the interpretation ascribed to the term bioequivalent. Schering argues that a bioequivalent generic drug must possess comparable rates of absorption to its pioneer drug counterpart. Relying on Congress' use of "absorption" in describing both "bioavailability" and "bioequivalent," Schering contends that "bioequivalent," like "bioavailability," must be read as an exclusive definition. The FDA views "bioequivalent" drugs as drugs possessing comparable efficacy, which can be determined by any appropriate method, that may, but does not necessarily, include measurements of drug absorption. Rather than providing the intended clarification, these seemingly plausible technical explanations advanced by the parties further illustrate the ambiguity of section 355(j)(7)(B).

[11] In *vitro* studies are conducted in an artificial environment such as in laboratory test tubes. *In vitro* tests do not measure absorption. *In vivo* studies are conducted in the human body to determine drug safety and effectiveness.

process absent absorption testing. Given the lack of evidence in the record regarding whether the effectiveness of NSEDs can be measured through absorption testing,[12] we are constrained to conclude based on the record before us that this provision is a further indication of the ambiguity of section 355(j)(7)(B).

The sparse legislative history of the Act regarding the intended meaning of bioequivalent does not alter our conclusion that section 355(j)(7)(B) is ambiguous. The only legislative history explaining bioavailability and bioequivalent is a footnote reference to the FDA's 1977 regulatory definitions of bioavailability and bioequivalent drug products, respectively codified at 21 C.F.R. §§ 320.1(a) and 320.1(e) (1977). H.R. Rep. No. 98-857, 98th Cong., 2nd Sess. pt. I, *reprinted in* 1984 U.S.S.C.A.N. at 2664.

IV.

Given our holding that section 355(j)(7)(B) is ambiguous, we must review the FDA's interpretation of that section to determine whether it is a permissible construction of the Act. *Chevron USA, Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837, 842-43 (1984). If the FDA's reading of the statute fills a gap or defines a term in a way that is reasonable in light of the congressional purpose in enacting the statute, we must defer to the FDA's interpretation. *See Nationsbank of North Carolina, N.A. v. Variable Annuity Life Ins. Co.*, —— U.S. ——, 115 S. Ct. 810, 813-14 (Jan. 17, 1995); *Sekula v. Federal Deposit Insurance Corp.*, 39 F.3d 448, 451-52 (3d Cir. 1994). In reviewing the FDA regulation interpreting the Act, we may draw from the language

[12] In fact, neither party could state with certainty whether the absorption of NSEDs could be measured through any means. Of course, we recognize that the FDA's position is that measuring the absorption of NSEDs is of no import in determining bioequivalence because NSEDs do not depend on absorption to derive their effectiveness.

of the statute, the legislative history, the agency regulations adopted to implement the statute and the agency comments regarding the regulations. *West v. Sullivan*, 973 F.2d 179 (3d Cir. 1992), *cert. denied*, —— U.S. ——, 113 S. Ct. 2934 (1993).

We find the FDA regulation interpreting section 355 (j)(7)(B) to be a reasonable construction of the Act. *See* 21 C.F.R. § 320.1(e) (1994). The legislative history expresses congressional desire that the Act provide a means for extending the abbreviated approval process for generic versions of pioneer drugs approved pre-1962 to generic versions of drugs approved post-1962. H.R. Rep. No. 98-857, 98th Cong., 2nd Sess. pt. I, *reprinted in* 1984 U.S.S.C.A.N. at 2647 The House Report provides:

> The purpose of Title I of the Bill is to make available more low cost generic drugs by establishing a generic drug approval process for pioneer drugs first approved after 1962. Under current law, there is a generic drug approval procedure for pioneer drugs approved before 1962, but not for pioneer drugs approved after 1962.
>
> Title I of the bill generally extends the procedures used to approve generic copies of pre-62 drugs to post-62 drugs. Generic copies of any drugs may be approved if the generic is the same as the original drug or so similar that FDA has determined the differences do not require safety and effectiveness testing.

Id. at 2647-48. *See also Drug Price Competition and Patent Term Restoration Act of 1984*, Senate Comm. on Labor and Human Resources, 98th Cong., 2nd Sess., 1 (June 28, 1984) (opening statement of Sen. Hatch: "The FDA currently has an ANDA practice for pre-1962 drugs. This bill extends that practice to post-1962 drugs."). Although the Act mandated a showing of bioequivalence for approval, there is no evidence that Con-

gress intended to limit the discretion of the FDA in determining when drugs were bioequivalent for purposes of ANDA approval. To the contrary, the expressed desire of Congress was to extend the then-current FDA abbreviated application practices to drugs first approved post-1962.

Congress' reliance on the FDA's 1977 regulations is significant. In addition to defining bioavailability and bioequivalent, the 1977 regulations set forth several studies and tests required for approval. *See* 21 C.F.R. §§ 320.23, 320.24, 320.53 and 320.57 (1990). These regulations are indicative of the "practice" Congress intended to extend to drugs first approved after 1962. The mere fact that Congress made the establishment of bioequivalence mandatory in the Act does not evidence an intent to limit the established testing practices of the FDA.

In adopting the challenged regulations, the FDA stated its disagreement with commentators that blood levels were always an appropriate or necessary measurement of bioequivalence. Abbreviated New Drug Application Regulations, Final Rule, 57 Fed. Reg. 17,950, 17,972 (April 28, 1992). Rather, the FDA stated its preferred method was to determine bioequivalence on a case-by-case basis depending on the drug under consideration for approval pursuant to an ANDA. *Id.* The FDA is the agency charged with implementing the Food, Drug and Cosmetic Act as amended. Its judgments as to what is required to ascertain the safety and efficacy of drugs fall squarely within the ambit of the FDA's expertise and merit deference from us. As such, the FDA's interpretation of section 355(j)(7)(B) as not limiting its discretion to determine what tests or studies would provide it with appropriate information from which to determine bioequivalence is a reasonable construction of the Act.

V.

Schering also challenged the district court's denial of its request that the FDA be enjoined from releasing, pursuant to section 355(1)(5), confidential safety and efficacy data (which Schering considers trade secret information) pertaining to Schering's pioneer NSEDs. 21 U.S.C.A. § 355(1)(5) (West Supp. 1994). *See supra* note 4. The FDA is required under the terms of section 355(1)(5) to release data at specific times for drugs named in an ANDA application. 21 U.S.C. § 355(1)(5) (West Supp. 1994).

Schering's request for injunctive relief was dependent on its position that NSEDs were not subject to approval through the ANDA process. Our affirmance of the FDA's interpretation of section 355(j)(7)(B), however, permits the approval of NSEDs through the ANDA process. Schering's request for injunctive relief based on the fact that the ANDA process did not apply to NSEDs, therefore, was appropriately denied.

VI.

Schering challenges the district court's conversion of the FDA's Motion for Judgment on the Pleadings to a motion for summary judgment pursuant to Rule 56 without providing Schering with a "reasonable opportunity" to respond as required by Rule 12(c) of the Federal Rules of Civil Procedure. Fed. R. Civ. P. 12(c) and 56. Schering's concern stems from the FDA's submission of the Declaration of Donald Hare with its reply to Schering's opposition to its motion and the uncertainty of whether the district court gave any weight to the factual Declaration in entering summary judgment in favor of the FDA. The district court did not address the Declaration in its opinion. The confusion results from the district court's incorporation of the reasoning of Judge Boudin's opinion, which is based on a different record and references the Declaration.

We have held that the district court, prior to converting a Rule 12 motion to a motion to a motion for summary judgment, must provide the parties with a reasonable opportunity to submit materials appropriate for a summary judgment proceeding. *See Ford Motor Co. v. Summit Motor Products, Inc.*, 930 F.2d 277, 284 (3d Cir.), *cert. denied sub nom, Altran Corp. v. Ford Motor Co.*, 502 U.S. 939 (1991). If notice is not given but the error is harmless, reversal is not required. *Id.* Here, Schering itself recognizes that the exclusivity of the statutory definition of bioequivalence is a legal question. The Declaration of Donald Hare was not material to our determination that section 355(j)(7)(B) is non-exclusive; therefore, we find that to the extent any error might have been committed by the district court, such error was harmless.

VII.

We will affirm the district court's entry of the summary judgment in favor of the FDA on grounds that section 355(j)(7)(B) is ambiguous but that the FDA interpretation of that provision embodied in its regulation at 21 C.F.R. § 320.1(e) (1994) is reasonable. We will also affirm the district court's denial of Schering's request for injunctive relief.

A True Copy:

Teste:

Clerk of the United States Court of Appeals
for the Third Circuit

APPENDIX B

[Filed Apr. 26, 1994]

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

Civ. No. 93-3493 (HLS)

SCHERING CORP.,
Plaintiff,

v.

FOOD AND DRUG ADMINISTRATION,
Defendant.

OPINION

Sarokin, District Judge

Before the court are plaintiff's motion for summary judgment and defendant's cross-motion for judgment on the pleadings.

Background

Schering Corporation ["Schering"], a manufacturer of certain "pioneer" drug products,[1] brings this action to challenge the Food and Drug Administration's ["FDA"] 1992 regulation under which generic competitors of pioneer drugs are approved. *See* 21 C.F.R. § 320.1(e). Title I of the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984) [the "Hatch-waxman Amendments" or "1984 Amendments"] to the federal Food, Drug, and

[1] A pioneer drug is the first drug product containing a particular active ingredient or ingredients to obtain FDA approval for a specified use.

Cosmetic Act, 21 U.S.C. §§ 301-394, provides an abbreviated new drug application procedure for FDA approval of generic drugs: the pioneer drug and its generic copy must be "bioequivalent" for FDA's approval without clinical testing to prove that the generic is safe and effective. 21 U.S.C. § 355(j)(7)(B).

The legislative history of the 1984 Amendments states that:

> The purpose of Title I of the bill is to make available more low cost generic drugs by establishing a generic drug approval procedure for pioneer drugs first approved after 1962.

Schering Corp. v. Sullivan, 782 F.Supp. 645, 650 (D.D.C. 1992), *vacated sub nom., Schering Corp. v. Shalala*, 995 F.2d 1103 (D.C.Cir. 1993); H.R.Rep. No. 857 (Part I), 98th Cong., 2d Sess. 14 (1984), *reprinted in* U.S. Code Cong. & Admin. News 1984, at 2647. However, Congress had another equally important consideration in mind—the safety of generic drugs approved through this abbreviated procedure. *See Tri-Bio Laboratories, Inc. v. U.S.*, 836 F.2d 135, 139 (3d Cir. 1987), *cert. denied*, 488 U.S. 818 (1988) ("The 1984 Amendments . . . reflect a statutory compromise of the competing concerns").

Prior to 1984, maufacturers desiring to sell generic copies of drugs approved after 1962 were required to submit full new drug applications. This involved a time consuming and expensive process which included comprehensive animal and human testing to show that the new drug is safe and effective. The 1984 Amendments free the manufacturer or distributor of a generic drug product from the clinical trial requirements as long as it could prove that the generic is bioequivalent to the already-approved pioneer drug it copies.

The Food, Drug, and Cosmetic Act provides two definitions of "bioequivalent," one of which is as follows:

> A drug shall be considered to be bioequivalent to a listed drug if—
>
> > (i) the rate and extent of *absorption* of the drug do not show a significant difference from the rate and extent of *absorption* of the listed drug when administered at the same molar dose . . . under similar experimental conditions . . . .

21 U.S.C. § 355(j)(7)(B) (emphasis added). The second definition provides for intentional differences in absorption rate from the listed drug.

The FDA's 1992 regulation defines "bioequivalent" as follows:

> the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes *available* at the site of drug action when administered at the same molar dose and under similar conditions in an appropriately designed study . . . .

21 C.F.R. § 320.1(e) (emphasis added). The FDA also provides for a second definition covering intended differences in rate of availability from the listed drug.

The FDA does not interpret the language of the 1984 Amendments as providing the two sole definitions of "bioequivalent." Rather, according to the FDA, the 1984 Amendments provide a "safe haven," such that if a generic meets one of the conditions defined therein, it must be deemed bioequivalent. A safe haven interpretation does not bar other means of determining bioequivalence, but under Schering's interpretation, the two definitions are the exclusive determinants of bioequivalence.

Schering manufactures certain non-systemically effective drugs ["NSED"s]. NSEDs, such as skin ointments or drug-containing mist inhalers, directly deliver the drug to the site of drug action, rather than through introduction

of the drug into the bloodstream. Schering claims that the FDA impermissibly diverged from congressional intent by substituting the broader concept of "availability" in the 1992 regulatory definition of bioequivalence for "absorption" as found in the 1984 Amendments. Schering's immediate concern is whether, as it argues, the abbreviated approval procedures is inapplicable to NSEDs which, by definition, do not depend upon systemic absorption to achieve their effect.

In December 1989, Schering filed a Citizen Petition which essentially argued that the bioequivalence requirement could be met only by satisfying one of the two showings set forth in Section 355(j)(7)(B); that such a showing could not be made for NSEDs under available scientific methods; and thus the FDA could not approve generic NSEDs via the abbreviated procedures. Schering initially brought suit in the United States District Court for the District of Columbia. *See Schering Corp.*, 782 F.Supp. 645. The district court ruled in favor of the FDA. However, while the case was on appeal, the FDA finalized its revised regulatory definition of bioequivalence. The circuit court ruled that this agency action mooted the challenge based upon the FDA's response to Schering's Citizen Petition and vacated the district court's judgment. *See Schering Corp.*, 995 F.2d 1103. The court suggested that a challenge to FDA's construction of Section 355(j)(7)(B) should best be brought in the context of the new 1992 regulations, and this case ensued. *Id.* at 1105.

Schering now moves for summary judgment and injunctive relief [2], and the FDA cross-moves for a judgment on the pleadings.

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[2] Schering requests that the court enjoin the FDA from releasing safety and efficacy data for its NSEDs. Section 355(l) provides that "unless extraordinary circumstances are shown" the

Discussion

The FDA's Standing Challenge

The FDA challenges Schering's standing to bring suit against its implementation of the 1984 Amendments. Schering's first counterargument is that the FDA, by regulation, has conferred standing upon it. Schering claims that its participation in the rulemaking process for the contested 1992 regulations satisfies the definition of "interested persons" such that Section 10.45(d)(1)(i) of Title 21, Code of Federal Regulations, confers standing upon it.[3]

The court agrees with the FDA's arguments that an administrative agency cannot circumvent the requirements for Article III standing nor the requirements for prudential standing where suit has been brought pursuant to Section 702 of the Administrative Procedures Act ["APA"].[4] The Supreme Court has held that the issue of standing is one of "interpreting congressional intent": " 'Congress can, of course, resolve the question [of standing] one way or another, save as the requirements of Article III dictate otherwise.' " *Clarke v. Securities In-*

FDA shall make available to the public the safety and effectiveness data upon which approval of a pioneer drug was based:

> (5) upon the effective date of the approval of the first application under subsection (j) of this section [the abbreviated procedure] which refers to such drug or upon the date upon which the approval of an application under subsection (j) of this section which refers to such drug could be made effective if such an application had been submitted.

21 U.S.C. § 355(l)(5).

[3] An "interested person is affected by, and thus has standing to obtain judicial review of final agency action . . . ." 21 C.F.R. § 10.45(d)(1)(i).

[4] Section 702 provides as follows:

> A person suffering legal wrong because of agency action, or adversely affected or aggrieved by agency action within the meaning of a relevant statute, is entitled to judicial review thereof . . . .

dustry Assn., 479 U.S. 388, 394 & n.7 (1986) (quoting *Association of Data Processing Service Organizations, Inc. v. Camp*, 397 U.S. 150, 154 (1970)) (citation omitted). The FDA cannot infringe upon congressional authority by removing prudential standing barriers through its regulations.

The FDA concedes that "[t]he loss of Schering's monopoly profits is an adequate allegation of injury-in-fact for purposes of Article III standing." Govt. Mem. at 13. Hence, the court turns to a consideration of prudential standing analysis. The Supreme Court first determined that Congress did not intend that every party suffering injury in fact has standing under Section 702 of the APA, the language of which grants standing to a person "aggrieved by agency action within the meaning of a relevant statute." 5 U.S.C. § 702. The Court then gave a "gloss" to the meaning of Section 702, requiring that

> the complainant be 'adversely affected or aggrieved,' *i.e.*, injured in fact, the additional requirement that 'the interest sought to be protected by the complainant [be] arguably within the *zone of interests* to be protected or regulated by the statute or constitutional guarantee in question.

Clarke, 479 U.S. at 395-96 (quoting *Data Processing*, 397 U.S. at 153) (emphasis added).

The Court refined its "zone of interests" test to deny standing where the interests of a plaintiff, who is not the subject of the agency's action, "are so marginally related to or inconsistent with the purposes implicit in the statute that it cannot reasonably be assumed that Congress intended to permit the suit." *Clarke*, 497 U.S. at 399. If a plaintiff is not subject to the regulation, it may still have standing if

> [it] can qualify as "protected" by a statute . . . [as either the] intended beneficiaries of the legislation or . . . what we have termed *suitable challengers*;

> that is, if their interests are sufficiently congruent with those of the intended beneficiaries that the litigants are not "more likely to frustrate than to further the statutory objective."

First Nat'l Bank and Trust Co. v. Nat'l Credit Union Adm., 988 F.2d 1272, 1275 (D.C.Cir.), *cert. denied sub. nom., AT&T Family Fed'l Credit Union v. First Nat'l Bank & Trust Co.*, 114 S.Ct. 288 (1993) (citations omitted).

The FDA argues that Schering's economic interest in protecting itself from competitors is "antithetical" to the purposes of the Hatch-Waxman Amendments which were designed to benefit the public with an increased choice of less expensive generic drugs. Govt. Mem. at 13. Schering, in its second counterargument to the FDA's lack of standing claim, argues in essence that it is a "suitable challenger" of the regulation. Schering contends that the cases which the FDA cites are concerned with a plaintiff's desire to protect itself from *existing* competitors whereas, in this case, Schering is seeking "only to enforce statutory 'entry restricting' requirements, like those involved in the FDA generic drug approval process." Pltf. Reply at 6-7.

The court determines that the abbreviated process acts as an "entry restriction" in that it sets a threshold, albeit a significantly lower one than the regular procedures, which generic drug makers must satisfy to obtain FDA approval. The court holds that Schering is a suitable challenger for standing purposes. Schering's situation is analogous to those presented in the cases it cites to support its position such that

> [t]he restriction connects the economic interests of competitors to the purposes of the statute and yet constrains competitors to a limited role in guarding a congressional drawn boundary. In these circumstances the plaintiffs can be thought to have interests

> "systematically aligned" with those the statute is designed to benefit.

First National, 988 F.2d at 1278.

For example, Schering emphasizes the *First National* court's language that "a plaintiff who has a competitive interest in confining a regulated industry within certain congressionally imposed limitations may sue to prevent the alleged loosening of those restrictions, even if the plaintiff's interest is not precisely the one that Congress sought to protect." 988 F.2d at 1277. Here, although Schering's interest in limiting the competition hinders Congress' desire to increase the public's access to less expensive generics, Schering's request that this court "patrol[] a statutory picket line" furthers Congress' twin desire to insure the safety of the generic drugs approved via the abbreviated procedures. *Id.* at 1278.

The *First National* court's focus upon the "congruence of plaintiffs' interest with those of the intended beneficiaries" of the legislation supports this interpretation. *Id.* at 1277. In both Supreme Court cases which the *First National* court analyzed, the plaintiffs' desires to limit entry converged with the legislation's purpose of protecting the intended beneficiaries from the dangers of too liberal policies, despite the fact that Congress did intend to protect those plaintiffs. *Id.* at 1276-77; *see also Clarke*, 497 U.S. 388;[5] *Investment Company Institute v. Camp*, 401 U.S. 617 (1971).

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[5] In *Clarke*, "the ever-vigilant securities industry was permitted to challenge a Comptroller decision that authorized a national bank to offer discount brokerage services not only at its established branches, but also at locations both inside and outside the bank's home state." *First National*, 988 F.2d at 1276. The legislation at issue "was designed to establish competitive equality between national and state banks and thus to protect smaller banks from competition from out-of-state leviathans, not to protect investment bankers." *Id.* The Supreme Court deemed that the plaintiffs had standing where their interests in squelching competition from national banks furthered the legislation's purpose of protecting state banks.

Hence, in *Investment Company*, the plaintiff investment bankers had standing to challenge "a ruling by the Comptroller of the Currency that would have permitted banks to slip the Glass-Steagall [Act] leash" where the Act "limited the securities underwriting and investment activities of banks . . . [in order] to protect bank depositors from risky bank activities—not to insulate investment bankers . . . from competition." [6] *First National*, 988 F.2d at 1276 (citation omitted).

The court concludes that Schering's interest in protecting its profits is congruent with one of two intertwined congressional concerns. Given the fact that Congress' desire to ease the entry of generics into the market exists in tension with its desire to guarantee the safety of those competitor drugs, the court determines that Schering should not be denied standing merely because its interests complement one but conflict with the other two congressional goals. The court does not reach the parties' other standing arguments and now turns to the merits of the statutory construction issue.

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[6] Schering also cites to several other cases which support its position. In *Data Processing*, the Court determined that data processing services have standing to challenge a ruling of Comptroller of the Currency permitting national banks to offer data processing services where the congressional act was designed to limit banks' activities to bank services. 397 U.S. 150.

In *Panhandle Producers v. Economic Reg. Admin.*, the court of appeals found that plaintiffs, an association "representing the interests of domestic gas producers, royalty owners and service companies, and its members," had standing to challenge the Economic Regulatory Administration's order granting a Canadian natural gas importer blanket authorization to import gas for two-year period pursuant to Section 3 of the Natural Gas Act. 822 F.2d 1105 (D.C.Cir. 1987). The court found prudential standing where plaintiff's interests in restricting entry into the domestic natural gas market arguably fit the statutory objectives of ensuring the import's competitiveness and protecting regional and national interests.

Summary Judgment and Judgment on the Pleadings Claims

This court can only grant summary judgment if there are no issues of material fact and, viewing the facts in the light most favorable to the non-moving party, the moving party is entitled to judgment as a matter of law. Fed. R. Civ. P. 56(c). *See Celotex Corp. v. Catrett*, 477 U.S. 317 (1986); *Wisniewski v. Johns-Manville*, 812 F.2d 81, 84 (3d Cir. 1987).

In light of the parties' submissions outside the briefing papers, the court will treat the FDA's motion to dismiss as a summary judgment motion. The court adopts the reasoning of Judge Boudin in the parties' identical case before him in the Federal District Court for the District of Columbia. *See Schering*, 782 F.Supp. at 648-51. Upon reviewing the parties' papers and Judge Boudin's opinion, the court concludes that Congress had not set forth an exclusive definition of "bioequivalent" in the 1984 Amendments. Accordingly, the court denies Schering summary judgment and grants the FDA summary judgment. Since the court rules in favor of the FDA on the merits, the court denies Schering's request for injunctive relief precluding the FDA from releasing Schering's safety and efficacy data.

/s/ H. Lee Sarokin
H. LEE SAROKIN
U.S.D.J.

Date: April 25, 1994

[Filed Apr. 26, 1994]

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

Civ. No. 93-3493 (HLS)

SCHERING CORP.,

Plaintiff,

v.

FOOD AND DRUG ADMINISTRATION,

Defendant.

ORDER

Before the court are plaintiff's motions for summary judgment and injunctive relief and defendant's cross motion to dismiss, which the court treats as a motion for summary judgment; and the court having considered the submissions of the parties; and for the reasons expressed in the accompanying opinion; and for good cause shown,

IT IS this 25th day of April 1994, hereby

ORDERED that plaintiff's motions for summary judgment and injunctive relief are denied; and it is further

ORDERED that defendant's summary judgment motion is granted.

/s/ H. Lee Sarokin
H. LEE SAROKIN
U.S.D.J.

APPENDIX C

UNITED STATES DISTRICT COURT
DISTRICT OF COLUMBIA

Civ. A. No. 90-1804(MB)

SCHERING CORPORATION,
Plaintiff,

v.

LOUIS W. SULLIVAN, *et al.*,
Defendants.

Jan. 17, 1992

MEMORANDUM OPINION

BOUDIN, District Judge.

The Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. §§ 301-394, provides that generic drugs may be approved pursuant to an abbreviated application procedure. 21 U.S.C. § 355(j). To receive such approval an applicant must show, among other things, that the generic drug is "bioequivalent" to a previously approved drug.[1] 21 U.S.C. §§ 355(j)(2)(A)(iv), (j)(3)(F). The

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[1] In scientific terms, drugs are considered bioequivalent if they "display comparable bioavailability when studied under similar experimental conditions." Bioavailability in turn "describes the rate and extent to which the active drug ingredient or therapeutic ingredient is absorbed from a drug product and becomes available at the site of the drug action." FDA, *Approved Drug Products With Therapeutic Equivalence Evaluations* 1-2 (10th ed.1990).

FDCA further provides that a new drug "shall be considered to be bioequivalent to a listed [i.e., previously approved] drug" if the rate and extent of absorption of the new drug do not significantly differ from the rate and extent of absorption of the listed drug, or if the extent of absorption of the new drug does not significantly differ from that of the listed drug and the rate of absorption of the new drug has been intentionally modified. 21 U.S.C. § 355(j)(7)(B).

The Food and Drug Administration ("FDA"), the federal agency responsible for administering the FDCA, decided that a generic drug may satisfy the bioequivalence requirement even if it does not satisfy the precise standards set forth in Section 355(j)(7)(B). *See* FDA Letter to Schering Corporation Responding in Part to Its Citizen Petition and Petition for Stay of Action Dated December 4, 1989 (June 4, 1990) ("FDA Decision"), Administrative Record ("AR") Tab 6. That section, says the FDA, simply creates a "safe harbor" for determining bioequivalence; that is, it ensures that, if one of the two specified showings is made, the new drug *must* be deemed bioequivalent to the approved drug. Plaintiff Schering Corporation ("Schering") contests this interpretation and claims that all applicants must make one of the two showings described in Section 355(j)(7)(B) in order to establish bioequivalence.

This case comes before the Court on Schering's and the federal defendants' cross-motions for summary judgment.[2] Oral argument was heard on April 30, 1991, and the matter was taken under advisement. On December 16, Schering moved to preliminarily enjoin the FDA's approval under Section 355(j) of a generic drug produced by Copley Pharmaceuticals, Inc. ("Copley"). Copley was granted leave to intervene in this action, and filed

[2] Intervenor-defendant Agvar Chemicals, Inc. also filed an opposition to Schering's motion for summary judgment.

an opposition to Schering's motion for a preliminary injunction. The Court heard oral argument on the latter motion on January 9, 1992.

The central issue presented by all of these motions is whether the FDA's interpretation of Section 355(j)(7)(B) is proper,[3] and the issue is a significant one with legitimate arguments on both sides. Since the Court concludes that the FDA's interpretation is consistent with the language of the FDCA and with its legislative history, the federal defendants' motion for summary judgment is granted. Schering's motion for summary judgment and motion for a preliminary injunction are denied, and its complaint is dismissed.

I. BACKGROUND

Schering manufactures and distributes a number of "nonsystemic" pharmaceutical drugs. In simple terms, a nonsystemic drug is applied directly to the site of the drug action (*e.g.*, ointment), rather than absorbed as a result of the drug's general dispersion throughout the body (*e.g.*, capsule).[4] On December 4, 1989, Schering petitioned the FDA to: (1) deny all applications for abbreviated approval of nonsystemic drugs; (2) refuse to disclose safety and efficacy data of nonsystemic drugs that have

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[3] The parties agree that FDA approval of the Copley product has mooted the ripeness question raised in the FDA's motion to dismiss, which was filed with its motion for summary judgment. Defendants further argue that the Copley approval would have been proper even under the narrow statutory interpretation being urged by Schering. Because the Court rejects Schering's reading of the FDCA, it need not consider this alternative argument.

[4] For example, Schering manufactures Lomitrin, "a topically administered antifungal agent," and Proventil, "an asthma relief medication administered through metered dose inhalers." Schering's Statement of Material Facts at 1, ¶ 2. Copley's albuterol sulfate solution for inhalation, the product which the FDA has approved and which Schering seeks to preliminarily enjoin, is being offered as a generic copy of Proventil.

been approved pursuant to the full application process; and (3) refuse to disclose the safety and efficacy data for Schering's nonsystemic drugs. Citizen Petition and Petition for Stay of Action from Schering Corporation ("Schering Petition"), AR Tab 1. In essence, Schering argued that the bioequivalence requirement could be satisfied only by making one of the two precise showings set forth in Section 355(j)(7)(B); that, under available methods of scientific experimentation, such a showing could not be made for nonsystemic drugs; and, therefore, that abbreviated applications for such drugs could not be approved. *Id.* at 3-4. Additionally, Schering argued that the FDA should not release safety and effectiveness data for approved nonsystemic drugs until generic versions can properly be approved pursuant to the abbreviated application process. *See* 21 U.S.C. § 355(*l*)(5).

On May 23, 1990, Schering submitted to the FDA supplemental documents in support of its contention that nonsystemic drugs presently cannot satisfy Section 355 (j)(7)(B). AR Tab 3. In light of the urgency of Schering's requested relief, the FDA elected to respond only to the legal questions raised by the petition, and to defer deciding the scientific questions. *See* FDA Decision at 1 n. 1. The FDA then concluded that the FDCA does not preclude approval of abbreviated applications for nonsystemic drugs. In particular, the FDA reasoned that Section 355(j)(7)(B) does not set forth the exclusive statutory definition of bioequivalence.[5] *Id.* at 6-7. Ac-

[5] The FDA also rejected Schering's argument that nonsystemic drugs are not "absorbed" and, therefore, cannot satisfy Section 355(j)(7)(B). It likewise decided that the rate and extent of absorption of a nonsystemic drug might be measured indirectly, and that such a measurement would satisfy Section 355(j)(7)(B). *See* FDA Decision at 6-12. Schering does not contest either of these conclusions, but does contest any suggestion that "bioequivalence" may be demonstrated by data that is not correlated, either directly or indirectly, to rate and extent of absorption. *See* Transcript of Summary Judgment Hearing at 14.

cordingly, the FDA denied Schering's request for relief. *Id.* at 21. Schering filed the present action on August 1, 1990.

Schering now challenges the FDA's interpretation of Section 355(j)(7)(B), and requests that the Court: (1) declare that Section 355(j)(7)(B) provides the exclusive definition of bioequivalence; (2) enjoin the FDA from approving any abbreviated applications for generic versions of nonsystemic drugs manufactured by Schering, and suspend the approval previously granted to Copley; (3) declare that Section 355(*l*)(5) does not require the disclosure of any safety and effectiveness data for nonsystemic drugs until it can be shown that those drugs satisfy the bioequivalence requirement; and (4) enjoin the disclosure of safety and effectiveness data for Schering's own nonsystemic drug products. Because the Court disagrees with the first proposition as a matter of law, and because the equities of this case do not support Schering's suggestion that it is entitled to emergency injunctive relief preliminary to a factual challenge of the Copley approval, the requested relief is denied *in toto*.

II. ANALYSIS

A. *Summary Judgment Motions*

Taking the legal issue presented to be ripe for adjudication, *see supra* note 3, it is also appropriate for summary judgment. Schering has raised a pure question of statutory interpretation, which is independent of any factual dispute and may be decided as a matter of law under Fed.R.Civ.P. 56. The parties appear to agree that the briefs submitted and argument presented suffice for a final decision on the merits of Schering's original complaint.

The first step in the Court's inquiry is to determine, using traditional tools of statutory construction, whether Congress had "an intention on the precise question at

issue." *Chevron USA, Inc. v. NRDC,* 467 U.S. 837, 843 n. 9, 104 S.Ct. 2778, 2782 n. 9, 81 L.Ed.2d 694 (1984); *Amalgamated Transit Union v. Skinner,* 894 F.2d 1362, 1368 (D.C.Cir.1990). If so, that is the end of the inquiry. In order to ascertain Congressional intent, the Court looks to the language in question, the structure of the statute as a whole, "and, where appropriate, legislative history." *Amalgamated Transit,* 894 F.2d at 1368. If, after undertaking such an analysis, the Court concludes that the statute is ambiguous or silent on the issue, it must defer to the agency's interpretation so long as it is reasonable and consistent with the purpose of the statute. *See Chevron,* 467 U.S. at 844-45, 104 S.Ct. at 2782-83.

Here, the intent behind Section 355(j)(7)(B) is clear from the language, structure, and legislative history of the 1984 amendments to the FDCA, all of which suggest that Congress permitted the FDA to retain its historically wide discretion in defining showings of "bioequivalence." Moreover, even if the statute had been ambiguous or silent on the issue, the Court nonetheless would be constrained to uphold the FDA's interpretation as a reasonable one, given the agency's established practice of accepting alternative showings of bioequivalence and the lack of any evidence that Congress intended to override that practice.

Section 355(j)(2)(A)(iv) of the FDCA requires an applicant for abbreviated approval of a generic drug to provide "information to show that the new drug is bioequivalent to the listed drug," unless the new drug has a different active ingredient, dosage form, route of administration, or strength than the listed drug.[6] *See* 21 U.S.C.

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[6] In the event that the new drug differs from the listed drug in one of the above respects, the applicant must petition FDA to receive an abbreviated application. 21 U.S.C. § 355(j)(2)(C). If that petition is granted, the applicant then must show (i) that the active ingredients of the new drug are in the same pharmaceutical

§§ 355(j)(2)(A)(iv), (j)(2)(C); *see also* 21 U.S.C. § 355(j)(3)(F) (abbreviated application may be insufficient to show bioequivalence). The only express statutory guidance for making this determination of bioequivalence is found in Section 355(j)(7), which reads in its entirety:

> For purposes of this subsection:
>
> > (A) The term "bioavailability" means the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from a drug and becomes available at the site of drug action.
> >
> > (B) A drug shall be considered to be bioequivalent to a listed drug if—
> >
> > > (i) the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses; or
> > >
> > > (ii) the extent of absorption of the drug does not show a significant difference from the extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the listed drug in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug.

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class as the active ingredients in the approved drug, and (ii) that "the new drug can be expected to have the same therapeutic effect as the [approved] drug." 21 U.S.C. § 355(j)(2)(A)(iv).

Standing alone, the plain language of Section 355(j)(7)(B) does not support Schering's argument that this section provides an exclusive test for establishing bioequivalence. The section does provide that a new drug "shall be considered to be bioequivalent to a listed drug" if either of the two specified showings are made. At the very least, this language means that, if an applicant makes one of the two showings, that applicant is statutorily entitled to a finding of bioequivalence It is far from apparent, however, that the language does anything more than delineate this "safe harbor." There simply is no indication that the enumerated showings are the exclusive means for establishing bioequivalence. In short, while the plain language of Section 355(j)(7)(B) does not foreclose the possibility that it sets forth the exclusive showings necessary to establish bioequivalence, at the same time that language does not, by itself, impose such a meaning.

The absence of language indicating that Section 355(j)(7)(B) provides the exclusive means for determining bioequivalence becomes significant when the two subsections of Section 355(j)(7) are read together. Subsection (j)(7)(A) provides that bioavailability "*means* the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from a drug or becomes available at the site of drug action" (emphasis added). Such language clearly indicates that "bioavailability" means what the statute says and no more. *See Weinberger v. Hynson, Westcott and Dunning, Inc.*, 412 U.S. 609, 630, 93 S.Ct. 2469, 2483, 37 L.Ed.2d 207 (1973) (similar language in 21 U.S.C. § 355(d) read to provide exclusive definition). An inveterate rule of statutory construction is that if one section of a statute contains a limiting term and a related section does not, the omission can be presumed intentional. *Russello v. United States*, 464 U.S. 16, 23, 104 S.Ct. 296, 300-01, 78 L.Ed.2d 17 (1983); *Adams v. Slonim*, 924 F.2d 256, 258 (D.C.

Cir.1991). Here, the inclusion of limiting language in subsection (j)(7)(A), in contrast with the absence of such language in subsection (j)(7)(B), suggests that subsection (j)(7)(B) was not intended to provide the exclusive definition of bioequivalence. Additionally, it is significant that, if Congress had so intended, ordinary boilerplate language could easily have been employed to give Section 355(j)(7)(B) the meaning urged by Schering. Indeed, comparable limiting language is found throughout Section 355. *See, e.g.*, 21 U.S.C. § 355(d) ("the term 'substantial evidence' *means* . . . .") (emphasis added).

Given the ease with which Section 355(j)(7)(B) could have been drafted to reflect an exclusive meaning, and given Congress' failure to employ limiting language in this instance, the Court is unwilling to read into the statute any terms that were not supplied by Congress. The Court concludes that Section 355(j)(7)(B) must be interpreted to mean what it says and nothing more: a drug shall be considered to be bioequivalent to an approved drug whenever either of the two showings set forth in that section is met. Thus, the plain language of Section 355(j)(7)(B), when read in light of the statute taken as a whole, itself provides sufficient support for the FDA's decision to deny the Schering Petition.

Moreover, not only does Section 355(j)(7)(B) fail to rule out the possibility that other showings might be used to establish bioequivalence, another section affirmatively suggests that they may. Section 355(j)(6)(A)(i)(III) gives FDA discretion to decide, for each listed drug, "whether in vitro or in vivo bioequivalence studies, or both such studies, are required for applications filed under this subsection. . . ." The reference to *in vitro*, or chemical dissolution studies, suggests a showing of bioequivalence that could be wholly detached from the focus on "absorption," i.e. absorption *in vivo*, in Section 355(j)(7)(B). At oral argument, Schering claimed that such *in*

vitro data is acceptable if and only if it is correlated to *in vivo* data. Transcript of Summary Judgment Hearing at 14. However, Schering also conceded that under the pre-existing regulations, bioequivalence could be demonstrated with *in vitro* data that was not correlated to *in vivo* data. *Id.;* 21 C.F.R. § 320.53(a)(5). This concession is significant because, as shown below, there is no evidence that Congress intended to reject this regulatory regime, and some evidence that it intended to adopt it.

The legislative history of the 1984 amendments to the FDCA, which enacted the abbreviated application procedure set forth in Section 355(j), indicates that Congress generally meant to accept the preexisting procedures for determining bioequivalence that were codified by the FDA in 1977. *See* 21 C.F.R. pt. 320. These rules governed abbreviated applications for the generic versions of listed drugs that had been approved by the FDA prior to 1962. The legislative history of the 1984 amendments states that:

> The purpose of Title I of the bill is to make available more low cost generic drugs by establishing a generic drug approval procedure for pioneer drugs first approved after 1962. . . . Title I of the bill generally extends the procedures used to approve generic copies of pre-62 drugs to post-62 drugs.

H.R.Rep. No. 857 (Part I), 98th Cong., 2d Sess. 14 (1984) U.S.Code Cong. & Admin.News 1984, p. 2647 ("House Report"). The last sentence of this passage evinces a clear intent to accept the FDA's then-existing methods of approving generic drug applications. Further, the legislative history's only reference to bioequivalence contains a direct citation to the 1977 regulations. *Id.* at 31, U.S.Code Cong. & Admin.News 1984, p. 2664.[7]

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[7] Schering argues that this specific reference to two sections of the 1977 regulations is indicative of Congress' intent to reject the remainder of the existing regulatory scheme. *E.g.*, Schering's Mo-

Under the pre-existing regulatory regime, FDA had discretion to require and to accept any of a variety of showings, ranging from *in vivo* testing in humans to *in vitro* testing uncorrelated to human *in vivo* data, as sufficient to establish bioequivalence.[8] 21 C.F.R. § 320.53. While the 1984 amendments did make the bioequivalence requirement mandatory, *see* 21 U.S.C. § 355(j)(2)(A)(iv), there is nothing in the legislative history to indicate that Congress also intended to restrict FDA's historical discretion to decide how that requirement would be met. *Cf. Mead Johnson Pharmaceutical Group v. Bowen*, 838 F.2d 1332, 1336 (D.C.Cir.1988). Given the lack of any evidence that Congress intended to effect such a policy shift, and in light of the evidence that Congress did intend to allow existing FDA procedures when it enacted the 1984 amendments, the Court finds that the legislative history supports its conclusion that Section 355(j)(7)(B) was not intended to be the exclusive definition of bioequivalence.

Moreover, even if the language, structure, and legislative history of Section 355(j)(7)(B) all could be viewed as ambiguous or silent on this issue, the Court holds that

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tion for Summary Judgment at 27-30. However, since other portions of the legislative history specifically refer to existing policies and regulations that the statute was intended to overturn, *e.g.*, House Report at 21, U.S.Code Cong. & Admin.News 1984, p. 2654, Schering's argument is at best inconclusive.

[8] Even in those cases where FDA determined that *in vivo* testing would be required, the regulations outlined a spectrum of possible showings, including, in order of preference: direct measures of drug absorption in blood or other bodily fluids; measurement of "an appropriate acute pharmacological effect," from which absorption could be inferred; and clinical trials to establish the safety and effectiveness of the drug. 21 C.F.R. §§ 320.57, 320.24 (1990). It bears noting that the third approach was not linked to measures of absorption, and thus was disfavored. Nevertheless, it was deemed "sufficiently accurate" for nonsystemic dosage forms such as the ones at issue in this case. *See* 21 C.F.R. § 320.24(c)(3) (1990).

the same absence of a Congressional intent to overhaul, rather than merely to refine and extend, a long-standing regulatory regime, would make the FDA's interpretation of the section a "reasonable" one. The Court likewise finds that the FDA's interpretation is consistent with the purposes of the FDCA. All the parties have expended a great deal of effort arguing that the dominant policy guiding construction of the statute is, on the one hand, to make more inexpensive generic drugs available to the public or, on the other hand, to ensure the safety of these drugs before they are substituted for their name-brand counterparts. However, the structure of the 1984 amendments to the FDCA makes evident, and other federal courts have held, that Congress had both objectives in mind. *E.g., Tri-Bio Laboratories, Inc. v. United States,* 836 F.2d 135, 139 (3rd Cir.1987) ("The 1984 Amendments . . . reflects a statutory compromise of the competing concerns."). Thus, the issue of statutory interpretation presented by this case cannot be resolved merely by having the Court choose between these two policies, which are in tension with one another, and both of which were of central importance to Congress. Instead, judicial review of specific abbreviated drug approvals, along with the underlying finding of bioequivalence, will remain an available avenue to strike the balance that Congress seems to have intended.

In this regard, the Court wishes to emphasize the limitations of the present holding. The fact that Section 355 (j)(7)(B) is not the exclusive definition of "bioequivalence" does not mean that the FDA is free to ignore bioequivalence altogether. First, as already discussed, the statute mandates that if an applicant makes one of the two showings enumerated in Section 355(j)(7)(B), the FDA has no choice but to find the generic drug "bioequivalent" to the listed drug. Second, Congress' enactment, at Section 355(j)(2)(A)(iv), of a mandatory bioequivalence requirement means that the FDA must make its bioequivalence finding under some reasonable

and scientifically supported criterion, whether it chooses to do so on a case-by-case basis or through more general inferences about a category of drugs or dosage forms.[9] In other words, the FDA's prior discretion not to impose any bioequivalence requirement, *see* 21 C.F.R. § 320.52, no longer exists. However, since the Court has found that Congress did not intend to restrict the FDA's discretion to determine how the bioequivalence requirement is to be met, the defendants' motion for summary judgment is granted, and Schering's motion for summary judgment is denied.

B. *Preliminary Injunction Motion*

In strictest terms, it would not appear that the Court, having ruled on the merits of the summary judgment motions, needs to reach any issue not raised by those motions. Even after Copley's product had been approved, Schering did not amend its complaint, but chose simply to cite the Copley approval as proof that the main issue of statutory interpretation was ripe for decision. *See supra* note 3. Thus, there is a sense in which resolution of that legal issue on its merits is dispositive of the preliminary injunction motion as well. On the other hand, something further needs to be said about the latter motion for two reasons. First, Schering has suggested, both in its reply brief and at the preliminary injunction hearing, that the FDA has not made a sufficiently supported record finding of "bioequivalence" for the Copley drug even under a

[9] Even under the 1977 regulations, FDA was required to find bioequivalence by "the most accurate, sensitive, and reproducible approach available." 21 C.F.R. § 320.24(b). In the case of drugs for which rate and extent of absorption are easily measured, that approach presumably will follow Section 355(j)(7)(B) closely. Thus, although the Court has found that Congress did not intend the two showings enumerated in Section 355(j)(7)(B) to play a larger role in the statutory scheme than they did in the regulatory scheme, the very presence of Section 355(j)(7)(B) in the statute also suggests that Congress did not intend for them to play a smaller role.

more expansive definition of that term. In light of this claim, it is at least arguable that Schering seeks to constructively amend its complaint to conform to new facts presently before the Court, scanty though those facts may be.

The second reason that the preliminary injunction motion must be addressed at greater length is that Schering, by intimating that the Copley drug potentially is harmful to the public, is seeking to raise the precise safety issue that was of concern to Congress. Procedural barriers notwithstanding, there can be little doubt that this Court would have a basis for enjoining shipment of the Copley drug if, for instance, it could be shown that the FDA likely had violated the FDCA in approving it and there were some significant evidence that the drug posed a health hazard ignored by the agency. Under the circumstances, it is prudent to discuss the merits of Schering's claims directed to the Copley product itself. For the reasons stated below, the Court finds that preliminary injunctive relief is not warranted on the present record.

When deciding a motion for a preliminary injunction, the Court must consider four criteria: (1) whether plaintiff is likely to prevail on the merits; (2) whether plaintiff has shown irreparable injury absent interim relief; (3) whether injunctive relief would significantly harm other interested parties; and (4) whether the public interest would be served by granting or denying preliminary relief. *Washington Metropolitan Area Transit Commission v. Holiday Tours,* 559 F.2d 841 (D.C.Cir.1977). The greatest difficulty with Schering's impromptu suggestion that it is entitled to preliminary relief even under a broad application of the statute is that it has not demonstrated a likelihood of success on the merits of a future factual challenge to the FDA's determination that the Copley drug is bioequivalent to the Schering pioneer drug.

Although Schering claims its challenge is "limited in scope" to FDA's asserted departure from what Schering

believes to be the statutory definition of bioequivalence, Reply Memorandum in Support of Motion for Preliminary Injunction at 6, Schering also suggests that, in any event, there is no adequate explanation underlying the FDA's finding or inference of bioequivalence. *Id.* at 8. However, the agency did purport to make such a finding or inference that the Copley drug is bioequivalent to the Schering drug, *see* Defendant's Opposition to Motion for Preliminary Injunction, Exhibit 2(c) at 1, and the FDA's affidavit—which is pertinent at the preliminary injunction stage—premises this determination on standards set forth by the 1977 regulations for drugs "administered by inhalation as a gas or vapor." *Id.*, Exhibit 2, ¶ 9; 21 C.F.R. § 320.22(b)(4). Apart from its statutory challenge, Schering has not yet offered an adequate basis for challenging the support for or the application of that regulation in this case.

Equally significant to the question of preliminary relief is Schering's failure to offer any affirmative evidence that there is reason for suspecting that the Copley drug would pose a threat to public safety. While much has been made about the general hazards of permitting non-bioequivalent generic drugs to be substituted for pioneer drugs, there is nothing before the Court, in the partial "administrative record" [10] or elsewhere, to suggest that the drug in question is such a drug and would have immediate harmful effects on the public. At the same time, the FDA's affidavit does describe the extensive review conducted by the FDA with the safety issue in mind. Here again, acknowledging the undoubted importance of the Congressional mandate for safe generic drugs, the Court cannot find on the present record that Schering would be likely to suc-

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[10] The FDA does not yet purport to have assembled the full administrative record relating to the Copley approval, and concedes that a future challenge by Schering based on that record would be permissible. *See* Defendant's Opposition to Motion for Preliminary Injunction at 5.

ceed on the merits of a future factual challenge to the Copley approval.

A preliminary injunction nonetheless might be warranted if the Court could find that Schering had "made a substantial case on the merits," and that the equities of the case "strongly favor interim relief." *Holiday Tours,* 559 F.2d at 843. However, as discussed, there is no evidence that the public interest would be served by issuance of an injunction, while delay in the marketing of Copley's drug could easily be against the public interest in reduced prices. *See Mead Johnson Pharmaceutical Group v. Bowen,* 655 F.Supp. 53, 56 (D.D.C.1986), *aff'd,* 838 F.2d 1332 (D.C.Cir.1988). Further, the Court finds that the equitable balance of harms between the parties is inconclusive at best. Schering argues that it will suffer great economic losses due to competition from the Copley product. This claim is speculative as to amount, *see id.* at 56, and in any event falls short of showing the immediate irreparable harm necessary to justify emergency injunctive relief.[11] Similarly, while Copley makes a credible showing that its economic interests could be irreparably damaged by an injunction, it is hard to accord great weight to this outcome where the facts suggest that Copley willingly assumed this risk when deciding to bring its product to market in the face of Schering's pending lawsuit. In sum, the Court concludes that the equities of the case do not warrant injunctive relief at this time.

Since the Court has ruled on the merits of Schering's original complaint, and concluded that there presently is no basis for the issuance of emergency injunctive relief,

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[11] Schering additionally claims that it would be harmed by the release of its safety and effectiveness data if the Copley approval is not enjoined. However, since Schering is entitled to independent judicial review of any FDA decision to release this data, it is not in danger of immediate irreparable harm from a possible disclosure. *See Mead Johnson,* 655 F. Supp. at 56.

Schering's complaint will be dismissed. The dismissal will permit Schering to seek immediate appellate review on the legal issue that both it and the FDA agree to be ripe. At the same time, this dismissal is without prejudice to any future suit that Schering chooses to bring for the purpose of challenging the Copley approval itself on a full administrative record.[12]

III. CONCLUSION

In accordance with this Memorandum Opinion, an Order will be entered this date, granting defendants' motion for summary judgment and dismissing this case, without prejudice to Schering's right to file a new action seeking judicial review of the Copley approval.

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[12] Alternatively, since Copley has a related action, *Copley Pharmaceuticals, Inc. v. Schering Corp.*, Civil Action No. 91-3189, pending in this Court, the parties may elect to use this action as the vehicle for obtaining judicial reveiw of the Copley approval.

APPENDIX D

STATUTES AND REGULATIONS INVOLVED

THE FEDERAL FOOD, DRUG, AND COSMETIC ACT AS AMENDED BY THE HATCH-WAXMAN AMENDMENTS OF 1984

12 U.S.C. § 355(j)(7):

For purposes of this subsection:

> (A) The term "bioavailability" means the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from a drug and becomes available at the site of drug action.
>
> (B) A drug shall be considered to be bioequivalent to a listed drug if—
>
> (i) the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses; or
>
> (ii) the extent of absorption of the drug does not show a significant difference from the extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple dose and the difference from the listed drug in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug.

21 U.S.C. § 355(*l*):

Public disclosure of safety and effectiveness data

Safety and effectiveness data and information which has been submitted in an application under subsection (b) of this section for a drug and which has not been previously disclosed to the public, shall be made available to the public upon request, unless extraordinary circumstances are shown—

(1) if no work is being or will be undertaken to have the application approved,

(2) if the Secretary has determined that the application is not approvable and all legal appeals have been exhausted,

(3) if approval of the application under subsection (c) of this section is withdrawn and all legal appeals have been exhausted,

(4) if the Secretary has determined that such drug is not a new drug, or

(5) upon the effective date of the approval of the first application under subsection (j) of this section which refers to such drug or upon the date upon which the approval of an application under subsection (j) of this section which refers to such drug could be made effective if such an application had been submitted.

REGULATIONS OF THE FOOD AND DRUG ADMINISTRATION

21 C.F.R. § 320.1 (a) and (e) (1977)

PART 320—BIOAVAILABILITY AND BIOEQUIVALENCE REQUIREMENTS

§ 320.1 Definitions

(a) "Bioavailability" means the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed from a drug product and becomes available at the site of drug action.

* * * *

(e) "Bioequivalent drug products" means pharmaceutical equivalent or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the therapeutic moiety under similar experimental conditions, either single dose or multiple dose. Some pharmaceutical equivalents or pharmaceutical alternatives may be equivalent in the extent of their absorption but not in their rate of absorption and yet may be considered bioequivalent because such differences in the rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body drug concentrations on chronic use, or are considered medically insignificant for the particular drug product studied.

* * * *

21 C.F.R. § 320.1 (a) and (e) (1992)

PART 320—BIOAVAILABILITY AND BIOEQUIVALENCE REQUIREMENTS

§ 320.1 Definitions

(a) *Bioavailability* means the rate and extent to which the active drug ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action.

* * * *

(e) *Bioequivalence* means the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study. Where there is an intentional difference in rate (e.g., in certain controlled release dosage forms), certain pharmaceutical equivalents or alternatives may be considered bioequivalent if there is no significant difference in the extent to which the active ingredient or moiety from each product becomes available at the site of drug action. This applies only if the difference in the rate at which the active ingredient or moiety becomes available at the site of drug action is intentional and is reflected in the proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug

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Supreme Court, U.S.
FILED
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No. 95-28

In the Supreme Court of the United States

OCTOBER TERM, 1995

SCHERING CORPORATION, PETITIONER

v.

FOOD AND DRUG ADMINISTRATION

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE THIRD CIRCUIT

BRIEF FOR THE RESPONDENT IN OPPOSITION

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QUESTION PRESENTED

Under the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 301 *et seq.* (FDCA), a drug manufacturer can receive approval from respondent Food and Drug Administration (FDA) for a new generic drug through an abbreviated application procedure (21 U.S.C. 355(j)), if the manufacturer establishes that the generic drug is bioequivalent to a drug previously approved by the FDA. The question presented is:

Whether the FDA's regulation, 21 C.F.R. 320.1(e), implementing one of the statutory bioequivalence provisions constitutes a reasonable interpretation of the FDCA.

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BRIEF FOR THE RESPONDENT IN OPPOSITION

OPINIONS BELOW

The opinion of the court of appeals (Pet. App. 1a-21a) is reported at 51 F.3d 390. The opinion of the district court (Pet. App. 22a-31a) is reported at 866 F. Supp. 821.

JURISDICTION

The judgment of the court of appeals was entered on April 3, 1995. The petition for a writ of certiorari was filed on July 3, 1995. The jurisdiction of this Court is invoked under 28 U.S.C. 1254(1).

STATEMENT

1. The Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 301 *et seq.* (FDCA), provides that manufacturers of new generic drugs can obtain approval for their products from respondent, the Food and Drug Administration (FDA), through an abbreviated application procedure, without the clinical testing that is necessary as part of a new drug application procedure. To obtain FDA approval for a generic drug under the abbreviated procedures, the manufacturer must establish, inter alia, that its generic drug is bioequivalent to a drug that previously was approved by the FDA. See 21 U.S.C. 355(b); 21 U.S.C. 355(j)(2)(A)(iv). Bioequivalence occurs "when two drugs possess the same efficacy." Pet. App. 5a.

The FDCA describes two circumstances in which a drug "shall be considered to be bioequivalent" to another drug. Section 355(j)(7)(B), which was added in 1984 as part of the expansion of the abbreviated application procedure, provides:

> A drug shall be considered to be bioequivalent to a listed drug if—
>
> (i) the rate and extent of absorption[1] of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental

---

[1] Absorption describes the process by which an active drug ingredient enters the body's physical system. Systemic absorption is the process by which a drug is introduced into the bloodstream, as occurs when a pill is taken orally or a drug is injected directly into the bloodstream.

conditions in either a single dose or multiple doses; or

(ii) the extent of the absorption of the drug does not show a significant difference from the extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the listed drug in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug.

21 U.S.C. 355(j)(7)(B).

In 1992, the FDA promulgated regulations implementing the bioequivalence requirements for generic drugs approved under the 1984 abbreviated application procedure. The regulation implementing subpart (i) of Section 335(j)(7)(B) defines bioequivalence as "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose and under similar conditions in an appropriately designed study." 21 C.F.R. 320.1(e).

2. Petitioner, a manufacturer of certain pioneer [2] drug products previously approved by the FDA, filed

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[2] A pioneer drug is the first drug product, defined by its particular active ingredient, to receive FDA approval for a specified use. Pet. App. 2a

suit in the United States District Court for the District of New Jersey claiming that the FDA's reguation defining bioequivalence, 21 C.F.R. 320.1(e), is invalid. Petitioner argued that the statutory provisions regarding bioequivalence, 21 U.S.C. 355(j)-(7)(B)(i) and (ii), constitute the only permissible definitions of bioequivalence and that these definitions call for an assessment of the actual absorption of drug products by the body. Petitioner contended that the FDA's regulation impermissibly broadens that statutory definition by replacing the statutorily prescribed measurement of drug absorption with a measurement that assesses when the drug becomes available at the site of action.[3]

The district court denied petitioner's motion for summary judgment and entered summary judgment for the FDA. Pet. App. 22a-32a.[4] The court adopted the reasoning of an earlier issued opinion of the United States District Court for the District of Columbia. *Schering Corp.* v. *Sullivan*, 782 F. Supp. 645 (1992), vacated as moot, 995 F.2d 1103 (D.C. Cir.

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[3] Petitioner argued that the bioequivalent standard based on absorption set forth in the FDCA could not be met for certain of its pioneer products that are non-systemically effective drugs, i.e. medications effective through topical application, such as ointments and mist inhalers. Therefore, under petitioner's interpretation and absent the FDA regulation defining bioequivalence to focus on availability, generic drugs claiming to be copies of petitioner's non-systemically effective drugs could not be approved through the abbreviated procedure because the abbreviated procedure requires the absorption bioequivalent determination. See Pet. App. 4a-5a.

[4] The district court rejected the FDA's challenge to petitioner's standing to maintain the action, as did the court of appeals. Pet. App. 26a-30a; *id.* at 13a.

1993) (set forth at Pet. App. 33a-49a). That opinion arose out of an action petitioner had commenced in 1989, seeking a declaration from the FDA that, inter alia, the bioequivalence requirement in the 1984 abbreviated application procedure could be met only by satisfying one of the two circumstances set forth in 21 U.S.C. 355(j)(7)(B). The district court in the earlier case had rejected petitioner's claim and entered summary judgment for the FDA.[5] Consistent with that ruling, the district court below granted summary judgment to the FDA, concluding that "Congress had not set forth an exclusive definition of 'bioequivalent.'" Pet. App. 31a.

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[5] Petitioner had petitioned the FDA in 1989 to deny all abbreviated applications for approval of non-systemically effective drugs. The FDA denied the petition and petitioner sought judicial review. The district court granted the FDA summary judgment. Pet. App. 33a-49a. The district court rejected petitioner's claim that 21 U.S.C. 355(j)(7)(B) provided the exclusive means for determining the bioequivalence required in the abbreviated application procedure. Pet. App. 43a. The court applied the two-step analysis in *Chevron U.S.A. Inc.* v. *Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984), and concluded that the congressional intent behind Section 355(j)(7)(B) is clear and that "Congress permitted the FDA to retain its historically wide discretion in defining showings of 'bioequivalence.'" Pet. App. 32a. The court also held, alternatively, that even if the FDCA is ambiguous or silent on the issue, the FDA's interpretation is valid because it is a reasonable interpretation in light of the absence of any evidence that Congress intended to override the FDA's practice of accepting alternative showings of bioequivalence. *Id.* at 38a, 43a-44a. The case ultimately was dismissed as moot on appeal, and the district court opinion vacated, in light of the intervening promulgation of the regulation, defining bioequivalence, which is at issue in this case. *Schering Corp.* v. *Shalala*, 995 F.2d 1103 (D.C. Cir. 1993).

3. The court of appeals affirmed. Pet. App. 1a-21a. Applying the two-step analysis in *Chevron U.S.A. Inc.* v. *Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984), the court held that the language of Section 355(j)(7)(B) is ambiguous, and that the FDA's regulation, 21 C.F.R. 320.1(e), is a permissible construction of the statute. Pet. App. 3a, 16a-19a.

With regard to the first step of the *Chevron* analysis—whether the statute is ambiguous—the court of appeals disagreed with the district court's conclusion that Section 355(j)(7)(B) unambiguously does not constitute an exclusive definition of "bioequivalent." The court of appeals also disagreed, however, with petitioner's argument that Section 355(j)(7)(B) is unambiguously exclusive. Instead, the court of appeals concluded that Section 355(j)(7)(B) is ambiguous.

The court acknowledged that Section 355(j)(7)(B) is couched in terms different from the immediately preceding Section, which unambiguously constitutes an exclusive definition of another term. See 21 U.S.C. 335(j)(7)(A).[6] Nonetheless, the court of appeals declined to find that the difference in language meant that Section 335(j)(7)(B) was unambiguously intended not to be an exclusive definition. The court found instead that the difference in language renders Section 355(j)(7)(B) ambiguous and that that determination is reinforced by other provisions of the FDCA that indicate that Congress envisioned the use

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[6] That Section provides:

> (A) The term "bioavailability" means the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from a drug and becomes available at the site of drug action.

21 U.S.C. 335(j)(7)(A).

of more than the one method of determining bioequivalence. Pet. App. 15a-17a. The court found that the legislative history of the 1984 Amendments that added Section 355(j)(7)(B) to the FDCA does not alter that conclusion.

Turning to the second step of the *Chevron* analysis—whether the agency's interpretation of the ambiguous statute is reasonable—the court of appeals agreed with the district court that the FDA's interpretation is a permissible construction of the FDCA. The court of appeals reasoned that the 1984 Amendments to the FDCA were intended to be a means for extending the abbreviated approval process, and there was no evidence that Congress intended to restrict the FDA's discretion in determining the bioequivalence of drugs for purposes of that process. Pet. App. 18a, citing H.R. Rep. No. 857, 98th Cong., 2d Sess. Pt. I (1984). The court emphasized the fact that, in enacting Section 355(j)(7)(B) in 1984, Congress relied on the FDA's 1977 regulations which indicated that different means could be used to determine bioequivalence.[7] The court recognized that Congress intended through the 1984 Amendments to extend that approach to generic drugs copying drugs first approved after 1962. Pet App. 19a.[8] The court found that

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[7] The FDA's 1977 bioequivalence regulations, 21 C.F.R. 320.1-320.62, applied both to drugs intended for systemic absorption and to non-systemically effective drugs, and provided for bioequivalence to be established by means other than actual measurement of rate and extent of absorption for non-systemically effective drugs. See 21 C.F.R. 320.22, 320.24, 320.53, 320.57 (1977).

[8] Before the addition of Section 355(j)(7)(B) as part of the broadening of the abbreviated application procedure in 1984, the

the FDA's preferred method "was to determine bioequivalence on a case-by-case basis depending on the drug under consideration for approval pursuant to an * * * abbreviated application." *Ibid.* It concluded that "[t]he FDA is the agency charged with implementing the Food, Drug and Cosmetic Act as amended. Its judgments as to what is required to ascertain the safety and efficacy of drugs fall

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procedures for FDA approval of a generic drug depended on whether the drug being copied had been previously approved by the FDA before 1962. Before 1962, the FDA had approved a new drug if it was safe for its intended use. The Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780, however, required manufacturers of new drug products to demonstrate that their products were not only safe but also effective for their intended uses in order to obtain FDA approval. After the 1962 Amendments, the FDA conducted its own examination, through the Drug Efficacy Study Implementation program (DESI), to determine whether the drugs it had approved as safe before 1962 were effective. See *Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 613-615 (1973). In light of these determinations of efficacy, the FDA decided to accept abbreviated new drug applications for generic copies of drugs it had found to be effective under the DESI program. The FDA required the abbreviated applications to contain information demonstrating that the product was bioequivalent to the previously approved drug. Full new drug applications were still required for generic versions of drugs first approved after 1962, however, because they had not been subject to DESI review. See *Tri-Bio Laboratories, Inc.* v. *United States*, 836 F.2d 135, 138 (3d Cir. 1987), cert. denied, 488 U.S. 818 (1988). Thus, the 1984 Amendments were intended to extend the abbreviated approval process for generic drugs to generic drugs that copied drugs approved after 1962.

squarely within the ambit of the FDA's expertise and merit deference from us." *Id.* at 19a.[9]

ARGUMENT

Petitioner contends (Pet. 16-23) that the court of appeals' opinion is contrary to the language, structure and history of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 301 *et seq.*, and that 21 U.S.C. 355(j)(7)(B) unambiguously establishes an exclusive definition of bioequivalence. Pet. 17-18. Petitioner contends (Pet. 23-27) that the court of appeals erred in upholding the FDA's regulation, 21 C.F.R. 320.1(e), as a permissible interpretation of the FDCA because the court "fundamentally misunderstood" the congressional purpose behind the addition of Section 355(j)(7)(B) to the FDCA in 1984. Pet. 25.

The court of appeals correctly rejected petitioner's arguments, as did the two district courts that have addressed them. The court of appeals' opinion reflects a straightforward—and correct—application of this Court's precedents on statutory construction. Petitioner acknowledges that there is no relevant circuit conflict. Pet. 15-16.

Section 355(j)(7)(B) cannot reasonably be read as an unambiguous statement of an exclusive definition.

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[9] Petitioner also had sought injunctive relief to prohibit the FDA from releasing certain safety and efficacy data regarding its products. See Pet. App. 7a n.4. That request for relief was dependent on a favorable finding on the merits and was therefore denied by the district court and the court of appeals. *Id.* at 7a n.4, 20a. The court of appeals also rejected petitioner's challenge to the district court's treatment of the FDA's motion for judgment on the pleadings as a motion for summary judgment. *Id.* at 20a-21a. Petitioner does not raise these issues in this Court.

See Pet. App. 13a-17a. Section 355(j)(7)(B) sets forth two circumstances in which a drug "shall be considered" to be bioequivalent to another drug. The Section's plain language does not state that the meaning of "bioequivalent" is limited to those two circumstances. In contrast, the immediately preceding Section of the statute contains limiting language and is couched in terms of what that term "means." See 21 U.S.C. 355(j)(7)(A). Moreover, as the court of appeals recognized, other Sections of the FDCA implicitly acknowledge that other means of determining bioequivalence are permitted. Those Sections reinforce the conclusion that Section 355(j)(7)(B) is not an unambiguous, exclusive definition of bioequivalence. See Pet. App. 16a-17a, citing 21 U.S.C. 355(j)(6)(A)(i)(III).

Thus, the language and structure of the FDCA are consistent with the FDA's interpretation that Section 355(j)(7)(B) functions as a safe harbor. The Section establishes two circumstances in which the FDA is required to find that a drug is a bioequivalent, but the statute permits the FDA to determine bioequivalence using additional methods.

The history of the 1984 Amendments to the FDCA also supports the FDA's interpretation. By adding the broader abbreviated application procedure in 1984, Congress intended to make available a greater number of safe and effective low-cost generic drugs. Congress sought to achieve this goal by extending the abbreviated application procedure and requiring a finding of bioequivalence as a part of the procedure, but it did not dictate the exclusive means by which the bioequivalence finding must be made. Pet. App. 18a. Most significantly, "[a]lthough the [1984 Amend-

ments] mandated a showing of bioequivalence for approval, there is no evidence that Congress intended to limit the discretion of the FDA in determining when drugs were bioequivalent for purposes of [the abbreviated] approval. To the contrary, the expressed desire of Congress was to extend the then-current FDA abbreviated application practices to drugs first approved post-1962." Pet. App. 18a-19a.

The FDA's method for determining bioequivalence relies on a case-by-case approach that depends on the charactristics of the drug under consideration. Absent an expressed contrary congressional intent, that judgment of the agency charged with implementing the FDCA merits deference. Pet. App. 19a. The court of appeals properly recognized the "considerable weight [that] should be accorded to an executive department's construction of a statutory scheme it is entrusted to administer, and [that] the principle of deference to administrative interpretations 'has been consistently followed by this Court whenever decision as to the meaning or reach of a statute has involved reconciling conflicting policies'." *Chevron*, 467 U.S. at 844 (footnote omitted). The FDA's "judgments as to what is required to ascertain the safety and efficacy of drugs fall squarely within the ambit of the FDA's expertise and merit deference." Pet. App. 19a.

CONCLUSION

The petition for a writ of certiorari should be denied.

Respectfully submitted.

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SEPTEMBER 1995

No. 95-28

Supreme Court, U.S.
FILED
SEP 11 1995
CLERK

IN THE
Supreme Court of the United States
OCTOBER TERM, 1995

SCHERING CORPORATION,
Petitioner,
v.
FOOD AND DRUG ADMINISTRATION,
Respondent.

On Petition for Writ of Certiorari to the United States Court of Appeals for the Third Circuit

PETITIONER'S REPLY BRIEF

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RULE 29.1 STATEMENT

Petitioner incorporates by reference the rule 29.1 statement set forth in the Petition for Certiorari at i.

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PETITIONER'S REPLY BRIEF

ARGUMENT

FDA's Brief in Opposition ("Opp.") confirms that the decision of the court of appeals is as significant as Schering stated in its Petition and that this case is fit for review by this Court. There is now no question as to the potential reach of the court of appeals' holding: FDA is not bound by a congressional standard of safety or efficacy in the approval of any generic drug sold in this country. This holding undoes a critical safeguard of the landmark Hatch-Waxman Amendments. Generic drug approvals continue unabated, and review of FDA's erroneous and self-serving view of that statute should occur without delay.

FDA appeals repeatedly in its Opposition to the deference owed an agency's construction of an ambiguous statute, but this is not a case about deference. Rather,

the question presented is whether FDA should be permitted administratively to reclaim authority specifically taken from it by Congress in 1984—the authority to approve generic drugs even if they are not bioequivalent to the pioneers which they copy. Clearly FDA has no such authority and its assertion of that authority under the guise of purporting to give "bioequivalence" a flexible meaning should have been rejected by the court of appeals. It was not, because that court, following FDA's lead, failed to address substantial affirmative statutory evidence confirming that Congress understood that it was writing into the statute the one, fixed definition that bioequivalence had historically enjoyed. FDA's Opposition glosses over the shortcomings of the court of appeals' decision, and is unresponsive to the overwhelming majority of arguments made in the Petition.

I. THE THIRD CIRCUIT'S JUDGMENT THAT THE HATCH-WAXMAN AMENDMENTS DO NOT ESTABLISH A JUDICIALLY-ENFORCEABLE STANDARD FOR HEALTH AND SAFETY IN THE APPROVAL OF GENERIC DRUGS BY FDA IS CONTRARY TO THE STATUTE'S PLAIN LANGUAGE, STRUCTURE, AND LEGISLATIVE HISTORY

It does not take long to respond to the only plain language argument that is made in the Opposition. That argument is a simple syllogism: the definition of "Bioavailability" (Section 355(j)(7)(A)) employs the word "means," and is exclusive; the definition of "Bioequivalence" (Section 355(j)(7)(B)) does not, and therefore it must be non-exclusive. Opp. 6. This is not statutory analysis, however, but an exercise in question-begging. The use of "means" certainly connotes an exclusive definition, but the language used by Congress to define bioequivalence *also* connotes an exclusive definition, and indeed has been used to introduce other exclusive definitions in the Food, Drug, and Cosmetic Act ("FDCA"). *See* Pet. 17-18. There is no textual basis for choosing one

definitional formulation over another or, more to the point, for claiming that only one and not both definitions can be exclusive.

FDA's focus on the absence of "means" in the definition of bioequivalence is perhaps the most improbable and insubstantial argument that could be launched, and only highlight's the agency's failure to address—even to *mention*—its own 1977 regulation defining bioequivalence. This regulation was the model for the statute and the predecessor of the regulation presently at issue. Schering and FDA agree that Sections 355(j)(7)(A) and (j)(7)(B) codified "almost verbatim" and "in all pertinent respects" FDA's 1977 regulatory definitions of bioavailability and bioequivalence, respectively, which were in force in 1984. *See* Pet. 19; J.A. 19, 27. Both of those definitions, however—*including the definition of bioequivalence*—employed the word "means," and were understood by FDA to set forth an exclusive, absorption-based definition. *See* Pet. 19; App. 52a. How could an exclusive definition—one that even contains the talismanic word "means"—be codified and yet lose its exclusive character? Neither FDA nor the court of appeals answers this question, or even refers to the regulatory definition (21 C.F.R. § 320.1(e) (App. 52a)) on which the statutory term is based.[1]

So far as statutory structure is concerned, FDA merely endorses without discussion the court of appeals' erroneous conclusion that another provision of the Hatch-Waxman Amendments, 21 U.S.C. § 355(j)(6)(A)(i)(III), "suggests" (J.A. 16a) that bioequivalence need not

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[1] The disappearance of the word "means" upon the codification of FDA's regulatory definition of bioequivalence is easily understood as an artifact of drafting. The 1977 regulation formally defined "bioequivalent drug products." Congress rephrased it to define when drug products are "bioequivalent," perhaps to be more parallel with the unchanged definition of "bioavailability," and in the process the word "means" became inappropriate and superfluous. *Compare* App. 52a *with* App. 50a.

be based on absorption. That section, however, is not a definitional provision. Rather, it requires FDA to publish a list of every approved drug product and state for each *how* bioequivalence may be shown, either by *in vitro* (test tube) or *in vivo* (in the body) tests. FDA asserted that *in vitro* tests cannot measure absorption, and because Congress recognized that an *in vitro* bioequivalence test might be used, the court of appeals inferred that absorption cannot be essential to bioequivalence. But the premise is flat wrong: *in vitro* tests may indeed show absorption, when they are correlated with *in vivo* tests and therefore are probative of whatever *in vivo* tests may show. Indeed, FDA contemporaneously with passage of the Hatch-Waxman Amendments declared that it would only accept *in vitro* tests that were so correlated.[2] Merely acknowledging that an *in vitro* test may be used to show bioequivalence is thus no evidence that a measurement of absorption is unnecessary.

What the court of appeals did not recognize about the statutory structure, and what FDA ignores entirely in its Opposition, is that the presence of the companion and concededly exclusive definition of bioavailability in Section 355(j)(7)(A) proves that the court's conclusion was wrong. Bioavailability and bioequivalence, both of which had parallel exclusive definitions in FDA's own 1977 regulations, have in addition always been defined *in pari materia*. As FDA itself stated with commendable economy, and as the court of appeals recognized, "bioequivalence is universally understood to mean comparable bioavailability." App. 16a & n.10. In this Court, however, FDA contends that Congress, in the very process of attempting to codify the two provisions unchanged, cleaved them apart by transforming bioequivalence from a definition to a safe harbor. This is no mere matter of

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[2] *See* letter dated November 16, 1984 from Harry M. Meyer, Jr., M.D., Director, Center for Drugs and Biologics, FDA, to interested persons at Paragraph 7. Pertinent portions of the letter are reproduced in the attached Appendix.

semantics, but what this case is about: the practical difference between an exclusive definition, which limits agency discretion, and a "safe harbor," which is a grant of administrative discretion, is enormous. It has as its endpoint whether FDA may act without the discipline imposed by the threat of effective judicial review. How FDA can argue that Congress' created so fundamental a difference between bioavailability and bioequivalence while attempting to codify their prior meaning "in all pertinent respects" is inexplicable, and FDA does not even try.[3]

While these specific statutory provisions were overlooked in FDA's Opposition, the agency missed the forest as well as the trees. FDA acknowledges (Opp. 10) that Congress added a statutory bioequivalence requirement for the first time in 1984, but to read the Opposition one would conclude this was an irrelevant gesture in what was only a rubber-stamping of FDA's prior practices. Nothing could be further from the truth.

Understanding the statutory bioequivalence requirement is utterly crucial both to the post-Hatch-Waxman generic drug approval process and to the disposition of this case. Congress' imposition of the first mandatory, nonwaivable bioequivalence requirement in 1984 did not extend but fundamentally changed FDA's preexisting practice. Prior to passage of the statute, FDA was free to determine whether or not bioequivalence would be required in connection with a particular generic drug approval.

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[3] FDA incorrectly attributes to Schering the argument that nonsystemically effective drugs can never be subject to generic competition under an absorption-based bioequivalence standard. Opp. 4 n.3, 5 n.5. Schering makes no such argument. As FDA itself understands, *all* drug products—including NSEDs—are absorbed, J.A. 39, and thus are capable of satisfying the statutory definition of bioequivalence. While measuring the absorption of various products, including many NSEDs, has always presented dfficulties, there is no evidence whatsoever in the record to the effect that it cannot be done now or is not capable of being done in the future.

The agency could determine that the rigorous bioequivalence standard was unnecessary for a given product, in which case it was free to employ whatever lesser standard of similarity to the pioneer product that it deemed appropriate. If, however, FDA required a showing of bioequivalence, 21 C.F.R. § 320.1(e) (1977) set forth the one definition of bioequivalence which applicants had to satisfy. All this changed in 1984. After Hatch-Waxman, FDA had no choice but to require in every instance that a generic be shown bioequivalent to the pioneer it was copying. Pet. 4; attached Appendix ¶ 8.

FDA's pre-1984 authority not to require bioequivalence —to be free instead to vary its approval criteria on a case-by-case basis—is precisely the discretion the court of appeals has allowed FDA to steal back administratively.

II. FDA'S CONSTRUCTION OF THE BIOEQUIVALENCE REQUIREMENT IS NOT A PERMISSIBLE ONE

FDA, again with little more than citation to the court of appeals' decision, argues under the second prong of the *Chevron* test that Congress specifically intended to codify the agency's allegedly historical discretion to give bioequivalence whatever meaning it wished on a "case-by-case" basis, and that FDA's regulation thus must be reasonable. Opp. 10-11. FDA, however, does not and cannot support its erroneous characterization of either Congress' actions or its own.

First, FDA's reliance upon general statements that Congress intended to extend the then-existing generic drug approval process have no force as to the question presented in this case. As explained above, while the Hatch-Waxman Amendments codified certain of FDA's prior terms and procedures, it changed the law fundamentally by adding the bioequivalence requirement. Those changes, ignored by FDA and the court of appeals, are what this case is about.

Second, FDA's claim to have historically given bioequivalence a flexible meaning (Opp. 11) is undocumented, unattributed, and simply wrong. Of all the possible questions involving the generic drug approval process, none could be less subject to debate than FDA's understanding of the meaning of bioequivalence prior to 1984. That definition was established by a published regulation and was written in what FDA itself acknowledges were exclusive terms that required a showing of absorption. *See* Pet. 18-19; App. 52a. Neither FDA nor the court of appeals cites any evidence whatsoever to support the improbable claim that the regulatory definition was ignored.[4]

It also remains the case that FDA's construction is unreasonable because the agency has become too willing to sacrifice the statutory safety requirement in its pursuit of generic drug approvals. Quoting the court of appeals, FDA says to this Court that bioequivalence occurs "when two drugs possess the same efficacy." Opp. 2. Perhaps omitting the requirement of comparable *safety* from the drug approval process was a slip of the pen; mistake or not, the error is now part of the case law and will remain so unless the Petition is granted. In any event, that misstatement of the law is precisely the one that the court

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[4] FDA asserts in a footnote that FDA's 1977 bioequivalence regulations apply to both systematically effective and nonsystemically effective (topical) drugs, and that regulatory provisions in effect in 1984 "provided for bioequivalence to be established by means other than actual measurement of rate and extent of absorption." Opp. 7 n.7. Schering agrees that the 1977 regulations applied to all drugs, as do the ANDA provisions of the FDCA today. As to the regulations cited, it is enough to say that two (21 C.F.R. §§ 320.22 and .23 (1977)) refer to *bioavailability*. Bioavailability, then as now, can only be defined in terms of absorption (*see* Opp. 6, 10); FDA's claim that the regulations prove that measurement of absorption is unnecessary is thus quite obviously wrong. The remaining two provisions merely list permissible test methodologies to satisfy the contemporaneously adopted regulation defining bioequivalence exclusively in terms of absorption.

of appeals told FDA it had made elsewhere in arguing that the goal of the Hatch-Waxman Amendments to encourage generic competition took precedence over health and safety concerns. *See* Pet. 25-26, App. 12a-13a. FDA is wrong about the statute, and the court of appeals was wrong under the banner of *Chevron* to have written the error into law based upon a misguided notion of deference.

CONCLUSION

The Petition For Certiorari should be granted.

Respectfully submitted,

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APPENDIX

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

[Nov. 16, 1984]

Dear Sir or Madam:

We are sending you this letter as part of an effort to keep interested persons informed in a timely manner as to the Food and Drug Administration's policies, implementation procedures and interpretations with respect to the Drug Price Competition and Patent Term Restoration Act. This information is provided as a supplement to my October 11, 1984 letter which you should have received, and is in the format of questions that we have received and answers that we have given to those questions.

* * * *

7. Q. What type of bioequivalence requirement will be imposed on the ANDAs for drugs first approved after 1962?

   A. *In vivo* data will be required for single-source and post-1962 drugs until such time as a correlation between *in vivo* and *in vitro* standards can be established for individual drugs. *In vivo* requirements will also be continued on other drugs where they are currently imposed. Of course, waivers from bioequivalence studies may be granted for dosage forms and routes of administration that are by their nature bioequivalent (e.g., intravenous solution).

8. Q. Under the DESI program, certain drugs that posed methodology problems were granted a de-

ferral of the bioequivalence requirements. Will this policy continue?

A. The new statute appears not to permit deferrals of bioequivalence requirements. Therefore, demonstration of bioequivalence, whether *in vivo* or *in vitro*, will be required for all drugs.